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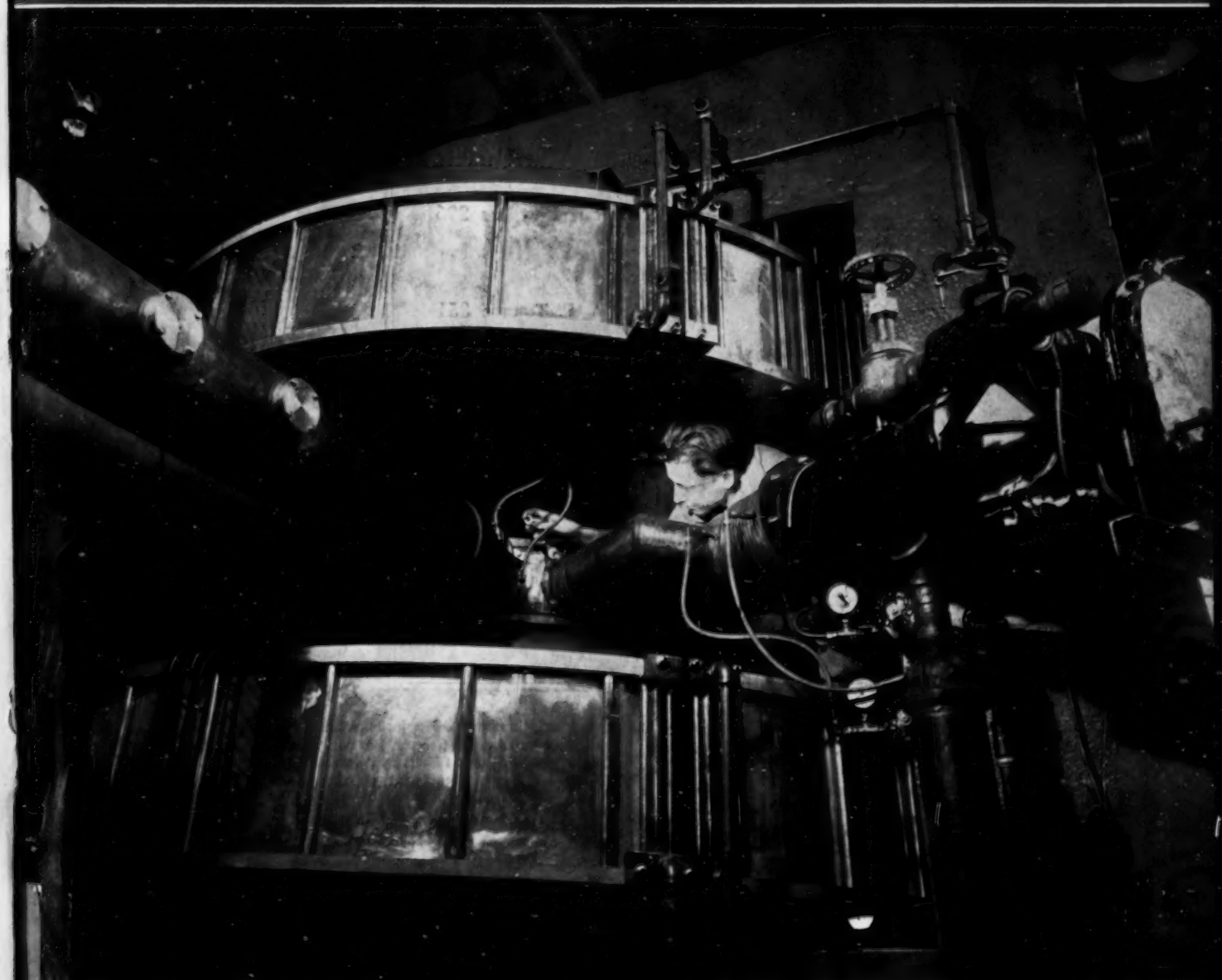
Vol. 12, No. 4 APRIL, 1941



The Cyclotron, One of the Tools of the Applied Nuclear Physicist

JOURNAL
OF
APPLIED PHYSICS

APRIL, 1941 Vol. 12, No. 4

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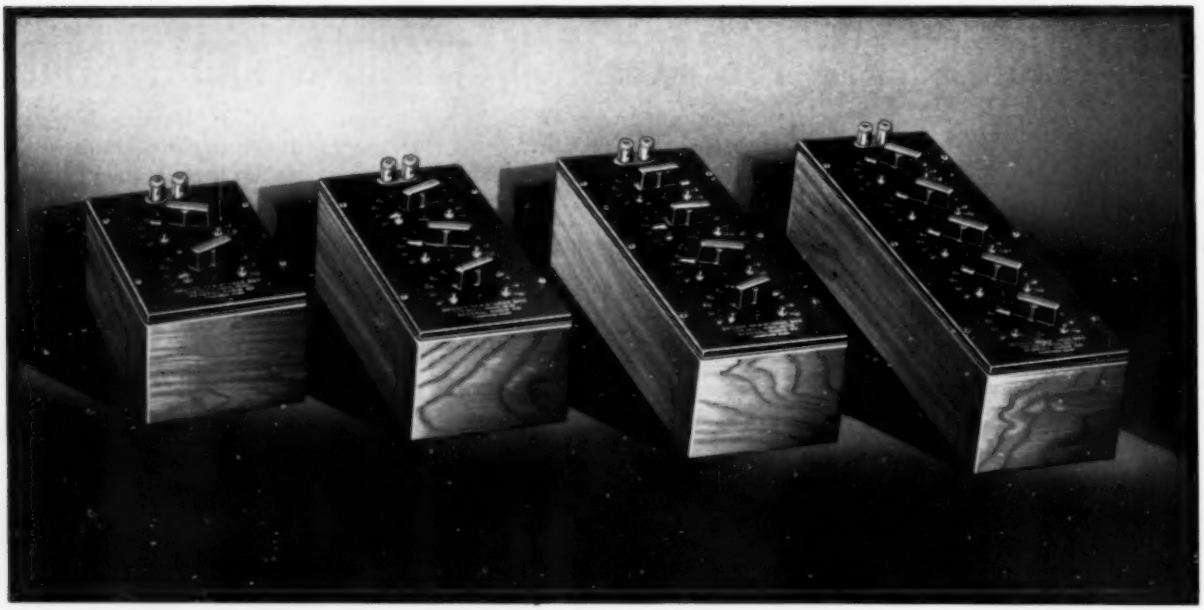

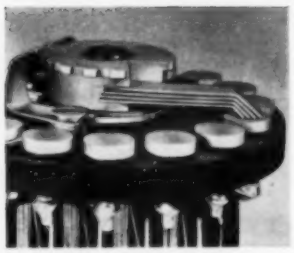

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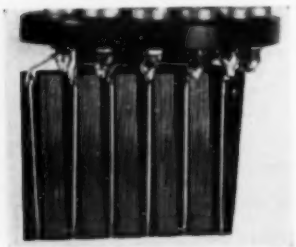

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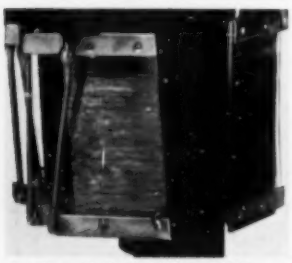

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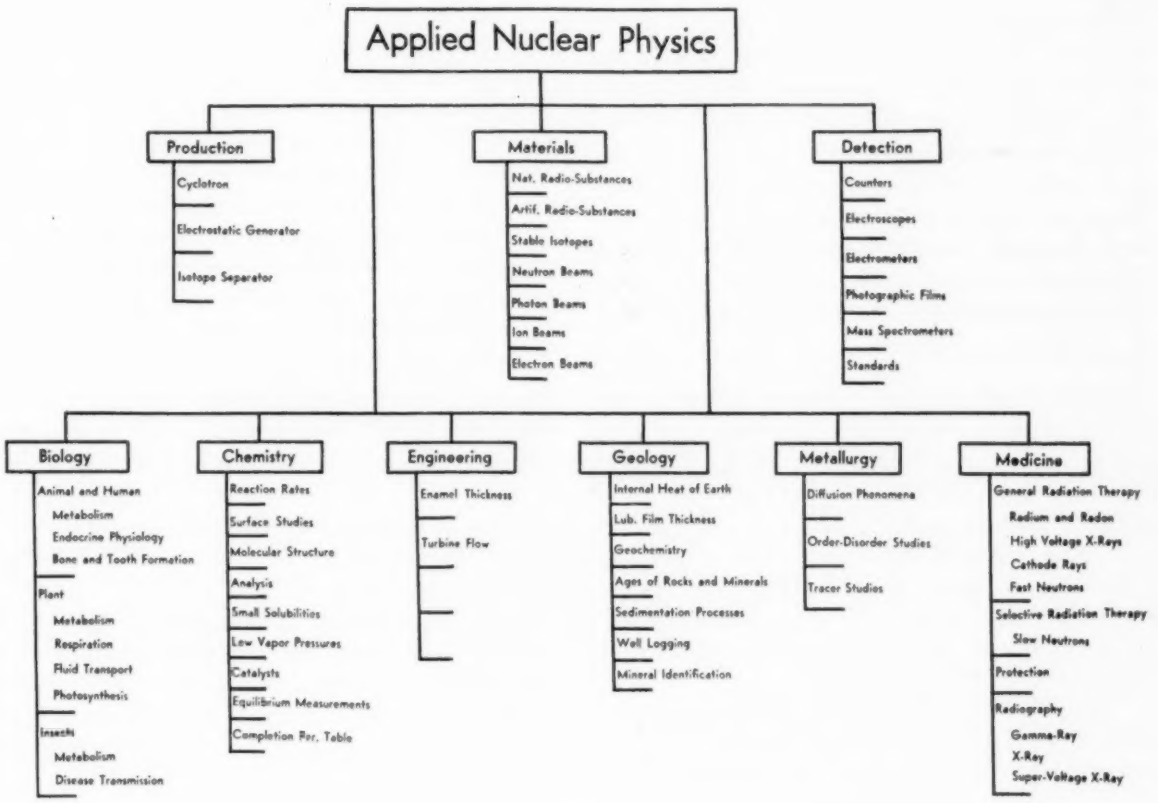
Volume 12 April, 1941 Number 4

Applied Nuclear Physics

THIS issue of the Journal is concerned primarily with the applications of nuclear physics. The great progress which has been made in this field in the past few years was made evident by the interest and the large attendance at the Conference on Applied Nuclear Physics last October. Special acknowledgment is due to the Program Committee of this Conference for their assistance in the preparation of this issue, and particularly to the Chairman of the Committee, Professor Robley Evans, who is a member of our editorial board.

To help in following the wide extent of the applications of nuclear physics, an outline of these is given below:



Applied Nuclear Physics*

BY ROBLEY D. EVANS

Massachusetts Institute of Technology, Cambridge, Massachusetts

Following the discovery of artificial radioactivity and the rarer stable isotopes of the light elements, the forty-year-old field of applied nuclear physics has found a greatly increased domain of usefulness in chemistry, metallurgy, radiology, geology, physiology and medicine. Isotopic tracer atoms, whether stable or radioactive, provide a powerful method for observing the behavior of complicated biological, chemical or physical systems under *equilibrium* conditions. Atom smashing machines, when slightly modified, are useful in metallurgical and clinical radiology, while other techniques and results from the field of nuclear physics find important applications in geology and astrophysics.

Introduction

NUCLEAR physics as an experimental science began on March 1, 1896 when Becquerel discovered the radioactivity of uranium. The field is thus about forty-five years old. During the first half of its life nuclear physics was confined almost exclusively to radioactivity.

Today the science of nuclear physics includes a large number of experimental and theoretical techniques for dealing with the nuclei of atoms, as well as the whole body of results from investigations using these tools. In addition to the basic properties of nuclei, their charge, mass, and moments, the field embraces all the physical and chemical properties of isotopes, the whole field of radioactivity, nuclear disintegration and synthesis, mass spectrometry, and the properties of corpuscular and electromagnetic radiation.

Applied nuclear physics connotes the application, beyond the normal domain of nuclear physics, of any knowledge, technique, or apparatus developed from work in the parent field.

Radium Therapy

The first applications of nuclear physics came shortly after the discovery of radium in 1898, and the subsequent preparation by the Curies of strong sources of radium. Through accidental burns to workers the biological action of gamma-rays was inferred and the field of medical radiology, especially cancer therapy, with radium got under way. Radium is now usually used in conjunction with x-ray treatment or with surgery, since few of the malignant diseases are manageable to best advantage by one agent or method alone. Radium or radon *implants*, in the form of small glass or gold seeds, are especially adaptable to intracavitary (e.g., the uterine cervix) and the interstitial (e.g., cheek or breast tumors) applications, where radium plays one of its most useful roles in curative medicine.

Geophysical Radioactivity

Historically, the second oldest applications of nuclear physics are in the geological sciences. As soon as the long lives of uranium and thorium were demonstrated, and the alpha-particle was identified with the helium atom, applications to the measurement of time were possible. About 1904 Rutherford suggested that the accumulation of radioactive decay products would offer a quantitative method for determining the geological age of individual specimens of material. Within two or three years Boltwood began measurements of geological age based on the accumulation of radiogenic lead in uranium and thorium minerals. Soon afterwards geological age measurements based on the accumulation of helium were undertaken by Strutt. All modern long period *geochronology* is based ultimately on geological age measurements by radioactive methods. In the solution of problems in historical geology, radioactive age measurements play a role of ever-increasing importance.

Age measurements by the lead method have been greatly improved in recent years through the accurate determination of lead isotopic abundance ratios by mass spectrometry. This has allowed more accurate discrimination between primal lead and lead produced by radio-

* Based on an address given at the joint meeting in Philadelphia on December 27, 1940 of the American Physical Society, the American Association for the Advancement of Science, and the American Association of Physics Teacher.

active decay.[1] Mass spectrometry has brought a new measure of accuracy and reliability to the field of geological age determination by the lead method.

About ninety-five percent of the earth's crust consists of igneous rocks. Geological age determination on this material can only be attempted on a basis of the accumulated helium, since the very low natural uranium and thorium content precludes the accumulation of a measurable amount of radiogenic lead. Much work has been done in recent years in improving the helium method of age analysis.[2] It has just recently been found that helium age analyses made on individual mineral constituents separated from igneous rocks may provide a trustworthy measure of geological age.

Hurley and Goodman have just shown that helium age analyses made on pyroxene and magnetite separated from an igneous rock can be relied on in many cases, whereas age analyses of the feldspar fraction or of the whole rock cannot be accepted.[3]

Of much interest in geophysics is the problem of the earth's internal heat. The measured radioactive content of the crustal rocks is sufficient to account completely for all of the heat which is known to escape from the earth by conduction through the rocks. Actually the amount of heat produced by radioactivity in the earth appears to exceed considerably the amount of heat escaping by conduction through the earth's crust, even when the energy liberated in volcanic action and earthquake activity is added. Slichter has shown that the very slow rate of travel of a thermal wave within the earth gives a satisfactory explanation of this apparent thermal anomaly. Actually the earth may be warming up slowly due to radioactive heating, rather than cooling down.[4]

Astrophysics

In astronomy, an important recent application of nuclear physics has been the explanation of the energy production in stars. Bethe has shown that a cycle of six nuclear reactions beginning and ending on C^{12} can account for the energy production and other related phenomena in ordinary stars.[5] The nuclear reactions, which fit the existing circumstances in the stars fairly quantitatively, involve the building up of helium out of hydrogen, with the use of C^{12} as a catalyst.

The origin of meteorites has been a puzzling astronomical problem for over a hundred years. Radioactivity has aided in the study of this problem by allowing age measurements to be made on these specimens of astronomical material.[6] Paneth has recently summarized all the evidence and has concluded that meteorites have been members of the solar system since their formation.[7] Many of the meteorite orbits resemble those of small asteroids. For all the elements which have been examined in meteorites the isotopic abundance ratio is the same as that found in terrestrial samples of the same element. This equality has recently been shown to hold also for the radioactive elements uranium[8] and potassium,[9] and the lack of any difference in these cases shows that the atoms in the meteorite were created at the same time as the atoms in the earth.

Isotopic Tracers

The use of tracer isotopes is one of the most widespread modern applications of nuclear physics. The method of radioactive indicators was a natural development from Madame Curie's initial radiochemical work, during the experiments on the discovery and separation of polonium and radium. As early as 1913 Paneth and Hevesy made the first applications of this method to chemical problems. During the years which followed they and their students made extensive investigations of the mechanism of exchange reactions, of oxidation-reduction couples, self-diffusion in lead, the metabolism of plants and animals, and many other problems in chemistry and biology.[10] Thus the groundwork and the fundamental principles of the method of tracer isotopes were all well worked out long before 1930. There were severe limitations on this early work because only the naturally radioactive isotopes were available, so the tracer experiments could only be done on lead (with RaD), bismuth (with RaE), and thallium (with AcC″).

The use of isotopes as tracers became a major field of applied nuclear physics during the middle and late 1930's. Only then were tracer isotopes of all the chemical elements discovered and made

available in quantities, together with the means for detecting them. Now more than 350 radioactive isotopes of all the known stable chemical elements are known.[11]

The present general usefulness of the tracer method therefore finds its origin first in the discovery of artificial radioactivity by the Curie-Joliots in 1934; secondly, in the perfection of the cyclotron by Lawrence and his collaborators who thus provided very strong sources of these new radioactive substances; and third, in the development of detection instruments, based on previous developments in other fields of radioactivity.

Parallel progress was being made simultaneously in the field of stable isotopes through first the discovery of the rare isotopes of hydrogen, carbon, nitrogen, and oxygen; secondly, the development of methods for separating these rare isotopes in useful quantities and in a nearly pure state, principally by Urey; and third, the perfection of mass spectrometers especially designed for rapid and accurate determinations of the relative abundance of isotopes.

Assumptions

It is well to re-examine the fundamental assumptions made in the use of isotopes for indicators. In every case it is assumed that the atomic weight difference between the marked and the ordinary isotopes in any particular element are *indistinguishable* to the chemical, physical, or biological system being studied. This assumption has been checked numerous times by measurements of the specific radioactivities, where radioactive tracers are used. Especially pertinent is the determination by Schoenheimer and Rittenburg of the relative abundance of the stable nitrogen isotopes, which is found to be the same in amino acids, proteins and air.[12] Similarly, Dole has shown that the ratio of the hydrogen isotopes is the same in honey, cholesterol, benzene and water.[13]

If radioactive isotopes are used as biological tracers, one must add the condition that all doses be kept sufficiently small so that the presence of radioactivity in the organism will not alter the physiological process being studied. Radiation effects must be studied in separate control experiments and all doses kept well below the measured *threshold for physiological effects*. This threshold varies considerably. For example, in the study of phospholipid metabolism in mice, a total dose of about thirty-six microcuries* of phosphorus per mouse may be used if only the brain is to be studied, but this dose will alter the metabolism in other parts of the body. If blood and muscle metabolism are to be studied, only sixteen microcuries of phosphorus may be used, while for liver studies only eight microcuries are allowable. The doses must be even smaller for chromosome work, because thirty percent of the chromosomes will be broken by a dosage of only eight microcuries per mouse.

It may be pointed out again that the radioactive tracer atom is perfectly normal until the radioactive transition occurs. Until its disintegration a radioactive isotope is indistinguishable chemically from other isotopes of the same element. For this reason it is sometimes preferable to speak of the method of radioactive "spies," since the words "tracer," "tagged atom," and "marked atom" connote the existence of a difference between the isotopes which is not actually present. The radioactive or separated stable isotopes are actually used as spies which go around unrecognized in the company of normal atoms of the same chemical type, and at a later time reveal the detailed movements of the normal atoms which they accompany. Ordinary experiments employ one spy atom for each 10^{10} to 10^{15} normal atoms whose course is to be traced.

Limitations

In extolling the great merits of the method of isotopic spies or tracers, it is well also to bear in mind the limitations of the method. In the use of radioactive isotopes there are two principal limitations. First, the total amount of radioactivity administered in physiological experiments must be kept below the biological threshold. This imposes a limitation on the *initial concentration* which can be used, and hence on the maximum dilution which can be detected in any particular experiment. Difficulties from this

* A *Curie* of any radioactive element exhibits 3.7×10^{10} disintegrating atoms per second.

source are usually not serious and can almost always be avoided by the use of highly sensitive detection apparatus. The second limitation is imposed by the *periods* of the radioactive isotopes, which are not subject to modification by man. Some elements have radioactive isotopes whose periods are too short to permit any but the simplest and quickest tracer experiments. Thus the radioactive isotopes of nitrogen have half-periods of only eight seconds and ten minutes, and these isotopes cannot be used for the study of intermediary metabolism of proteins.

There are also limitations on the use of separated stable isotopes as tracers. Thus far only the isotopes of hydrogen, carbon, nitrogen, oxygen, and sulphur are available for study. Of these the heavy isotope of nitrogen is, of course, of exceptionally great importance, for otherwise it might be impossible to study the intermediary metabolism of proteins and the amino acids. But only these five important elements are available for study with stable isotopes. Secondly, the allowable dilution factor is usually smaller than in the case of radioactive isotopes and is limited by that dilution which brings the original sample so close to the normal isotopic abundance that the difference cannot be distinguished experimentally. Thus for practical purposes C^{13} becomes lost after a dilution of ten thousand, whereas N^{15} cannot be determined after a dilution of thirty thousand, and H^2, after a dilution of about one hundred thousand.

In the past two years great progress has been realized in the application of the spy method to problems in metallurgy, chemistry, and biology. We may consider a few of these applications briefly in order better to understand the broad range of problems which can be attacked by this method.

Metallurgy

Diffusion

In metallurgy the process of diffusion plays a dominant role in such basic problems as the annealing of ingots and forgings, the determination of the directional properties of forgings, the constitution of annealed steel at high temperature, the rate of solution of carbides on high temperature annealing, and the embrittlement of copper. Diffusion is also a dominant process in powder metallurgy, where new alloys are prepared by annealing mixed metal powders.

The conventional diffusion coefficient is a measure of the rate of disappearance of a very small chemical inhomogeneity. With the use of spy isotopes it is possible to measure a much more fundamental type of diffusion, that is, one in which the chemical composition of the entire specimen is homogeneous at all times. It is possible, in principle, to measure the motility of any element in any homogeneous surroundings, no matter how complicated they may be. Thus the study of the atomic migration of radioactive copper in copper gives direct information about the movement of individual atoms in completely homogeneous surroundings. One can calculate directly from the measured diffusion the average number of elementary moves made by an atom during the time of the experiment. This can be compared with theoretical predictions based on various models for the place-change mechanism,[14] until a satisfactory model of this solid state is obtained. A moderate amount of work has already been completed on the self-diffusion of bismuth,[16] gold,[16] lead,[15] zinc,[16] and copper,[17] and this general field is certainly due for a rapid expansion in the near future.

Metallurgical Chemistry

In metallurgy there are a number of chemical reactions which can be evaluated quantitatively more quickly, and possibly more accurately, by the methods of isotopic spies than by conventional methods. Examples such as the corrosion factor in steam boiler tubes, and the rate of reaction in the formation of slag in blast furnaces are already being studied.

Radiography

In industrial radiography, the nondestructive testing of castings and forgings is now becoming close to universal practice. In many cases high voltage portable x-ray tubes have been used for this type of testing. The penetrating power of x-rays of the order of a half-million volts is sufficient only for the testing of material having a moderate thickness. On larger work the more penetrating gamma-radiation of radium or radon has been used extensively. In this con-

nection the relatively new radioactive isotope of yttrium may prove interesting industrially because its half-period of one hundred days is very much greater than that of radon, and its gamma-rays appear to be almost homogeneous with an energy of about two million volts, which is somewhat higher than the gamma-radiations from radium. If radio-yttrium could be made available cheaply and in sufficiently large quantities, it could be of considerable practical usefulness in the very greatly expanded industrial activities associated with the nation's defense.

It may be said in general that the higher voltage radiations have a higher penetrating power and can therefore be used on very thick material, but because of this high penetrating power they have a smaller resolving power than lower voltage radiations in the detection of minute flaws. Thus the choice of soft or hard radiation in industrial radiography depends upon a balance between the importance of resolution and penetrating power in the individual case at hand. The one-million-volt, pressure insulated, electrostatic generators developed by Trump and Van de Graaff[18] can be used to detect all flaws amounting to more than 2.5 percent of the thickness in 4-inch thick steel, with an exposure time of only about two minutes. Compact generators of this type for use above three million volts are now available.

Chemistry

General

In many chemical problems the method of radioactive spies is an exceptionally powerful tool. Exchange reactions may be studied under equilibrium conditions. The vapor pressure, solubility, and other physical properties, of substances which are otherwise difficult to measure, may be readily obtained.[19]

Artificial transmutation has gone far toward the completion of the periodic table. Elements 43 and 85 have been produced artificially and their chemical properties studied.[20] It is probable also that element 61 has been produced by the bombardment of neodymium with deuterons,[20] but because of the well-known difficulties of dealing chemically with the rare earths no separations have been attempted as yet. The other missing element, 87, has recently been identified as a rare branching product in the actinium series of naturally radioactive elements.[20]

Analysis

Tracer isotopes are being used in several laboratories in order to obtain greater sensitivity and more speed in the routine chemical analysis of complicated biological or industrial organics. The substance in question must first be synthesized using a tracer isotope. A small amount of this spy material is then mixed with the unknown. Then a small but pure fraction of the substance in question is separated from the unknown. This separation of a small but pure fraction is usually very much simpler and quicker than the quantitative separation of the entire amount of the substance. The small pure fraction is then analyzed for the tracer isotope; the reduction in its specific activity is a direct measure of the dilution which the spy substance has suffered, and hence of the amount of the substance originally present in the unknown. This method can also be used to extend the accuracy of microchemical techniques by about a factor of ten without great difficulty.

Catalysts

The tracer method is ideally suited to the study of adsorption phenomena, and to the investigation of surface catalysts. Studies of the mechanism of surface catalytic action in industrial chemical practice are being carried out in several commercial laboratories with the aid of radioactive tracers.

Physiology

Perhaps the most striking applications of the method of isotopic spies has been in the field of animal, plant, and insect[21] physiology. This is because the method provides for the first time a means of studying the metabolism of various nutrients and toxins while the organism is in a normal, healthy, equilibrium state.

Plant Nutrition

The method of the autoradiograph, originally developed to locate the zones of highest activity in sections of radioactive minerals, provides a

simple and graphic method for determining the gross distribution of radioactive substances in living tissues. After administration of the substance whose distribution is to be studied, a thin section of tissue is placed on a photographic film. The beta-radiations from the radioactive substance in the specimen sensitize the photographic film and produce an image which is directly proportional to the amount of radioactive substance at various points in the sample. The application of this method is well illustrated in the studies of phosphate nutrition in tomato plants.[22] To the nutrient solution in which a fruit-bearing tomato plant is growing, a small amount of radioactive phosphorus in the form of a phosphate is added. After a suitable period of time sections of the fruit are prepared and autoradiographs taken. When fruits of the same size and from the same plant are compared, it is found that the green fruits take up a much larger amount of the phosphate than do the ripe fruits. Also the concentration of phosphate is especially pronounced in the seeds of the green fruits, as shown in Fig. 1.

It has been found that plants are capable of effecting an exchange between the plant root and the very small colloidal clay particles of the kind found in the soil. Studies of this absorption process by a plant have shown for the first time that the nutrient cations can and do move in both directions between the roots and the clay particles.[23] Therefore the nutritional process of contact exchange must be divided into the two oppositely directed processes of contact intake and contact depletion of the root system.

The upward and lateral movement of salts containing potassium, sodium, phosphorus, and bromine have been studied in actively growing and transpiring willow and geranium plants.[24] These experiments have conclusively shown that the path of rapid upward movement of salt is in the wood, or xylem, of the plant, rather than in the bark. In addition to the rapid upward movement through the wood, there is a moderately rapid radial transfer from the wood to the bark.

With the aid of this new tool plant physiologists are already making rapid progress in the determination of the rates of absorption, paths of movement, and distribution within the plant of nutrient elements.

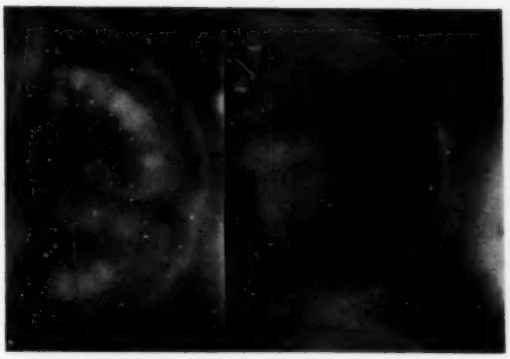


FIG. 1. Autoradiographs of quadrants of green (left) and ripe (right) tomato fruits of the same size and from the same vine, when radioactive phosphorus is present as phosphate in the nutrient solution. The green fruit is seen to have been absorbing phosphate more rapidly, especially in the seeds. (*Arnon, Stout and Sipos.*[22])

ANIMAL METABOLISM

With the aid of radioactive iron the fate of iron atoms in normal and in anemic animals has been studied exhaustively by Whipple, Hahn and their colleagues.[25] These experiments have disclosed a number of previously unknown facts concerning the metabolism of iron. In normal health the body clings very strongly to the iron which it contains and absorption and excretion are extremely small. Rapid absorption of iron takes place only in an anemic organism, that is, in one in which the need is great. Then the iron is absorbed almost exclusively from the gastro-intestinal tract and is transported by way of the plasma to the blood-producing centers where it is entirely made into hemoglobin in a very short time. There is no direct exchange of iron between the hemoglobin and the plasma. New hemoglobin containing radioactive iron is detectable in the blood within about four hours, and the absorbed iron is entirely made into hemoglobin in from four to seven days in anemic dogs. The fractional uptake is found to be greater for small doses. Radioactive red cells may be readily removed from one animal and introduced into another. In this way the breakdown of hemoglobin can be studied quantitatively.

The thyroid gland plays fundamental roles in the regulation of growth, and of body heat. Its hormonal secretions are rich in iodine, and the metabolism of this element, which appears to be of basic importance in the proper functioning of

the thyroid, is being studied in several laboratories with the aid of radioactive iodine.[26] Both normal and diseased thyroid glands are found to take up iodine from the blood stream within a few minutes after administration. The uptake is very much greater in the case of an enlarged

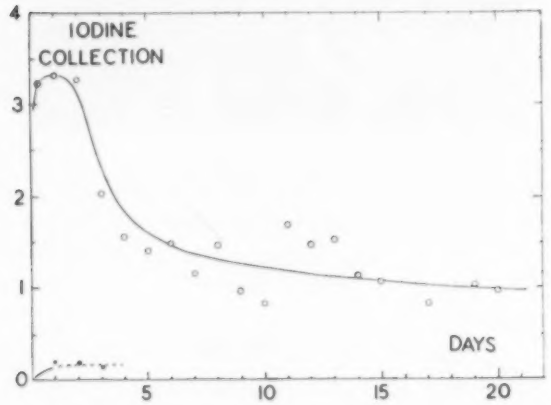


FIG. 2. The upper curve shows the average uptake of iodine by the thyroid gland in six cases of human toxic goiter, following the administration of about 1 mg of iodine containing radioactive iodine as a tracer. The lower curve shows the very much smaller accumulation in a normal human thyroid. (*Hertz, Roberts, Means and Evans.*)

(hyperplastic) gland, while for both normal and hyperplastic thyroid glands the fractional uptake of iodine increases as the size of the dose is diminished. In humans with toxic goiter the thyroid gland will take up (Fig. 2) practically all of the administered iodine if the dose is of the order of one milligram or less. Basic studies are in progress on the rate and mechanism of the conversion of the absorbed iodine into the various components of thyroid hormone.

Vitamin B_1 has been synthesized using radioactive sulphur, and studies of its storage, excretion and utilization have shown that ten percent of the vitamin B_1 in the human body is destroyed every twenty-four hours.[27]

Using radioactive carbon, Hastings and associates[28] have undertaken the study of carbohydrate metabolism. The formation in the liver of the important animal starch, glycogen, is found to involve a number of biochemical reactions whose course could not be correctly traced by older methods.

Using stable isotopes as tracers Schoenheimer, Rittenberg and their colleagues are continuing their brilliant series of experiments on the intermediary metabolism of fats, proteins, and amino acids.[29] All these experiments show a rapid and widespread turnover among the molecules in the living body. There is a continuous interconversion among the fatty acids in normal animals, and rapid chemical reactions are going on all of the time among all the body constituents of perfectly normal animals.

This rapid turnover is well illustrated by the observation, using stable isotopes of hydrogen and nitrogen, that normal rats absorb two-thirds of the nitrogen ingested in the form of the amino acid leucine, which is a constituent of protein. Yet only one-third of this absorbed nitrogen enters body protein molecules while still associated with its original leucine molecule. The remaining two-thirds of the absorbed nitrogen is deposited in the body proteins as a result of continuous nitrogen transfers from one amino acid to others.[30]

All of these metabolic experiments, taken either individually or collectively, have disclosed extremely general, rapid, and widespread turnover and interchange among the molecules in the living body. Enzymatic equilibrium or steady state reactions occur everywhere all of the time in the body.

In summarizing the tracer work, it should be emphasized that the method of isotopic spies provides a unique method for investigating a *normal animal or organism under equilibrium conditions*. Calorie balance and nitrogen balance can be maintained rigorously during the entire course of the investigation. That this is a great step forward can be appreciated when it is realized that previous knowledge of intermediary metabolism usually had to come from experiments performed under wholly abnormal conditions. It was necessary to use organisms which were sick or poisoned or from which certain tissues or organs had been removed. Abnormal or unnatural compounds had to be administered, or diets unduly enriched or impoverished in the test substances had to be employed. It is small wonder that the results of such experiments were necessarily fragmentary and often incompatible with one another. The entire field of physiology and biochemistry needs to be, and is being, re-examined with the aid of the powerful method

of isotopic spies. In many cases the new results already obtained are contrary to previously accepted viewpoints. These new results serve to clear away much dead wood and to give valid reasons for discarding many alternative or conflicting interpretations of old observations. Fortunately the investigators have usually chosen to examine fundamental problems. Their new results are serving to establish a firm basis on which biochemical and physiological knowledge can be rapidly and consistently enlarged.

Radiation Therapy

The tools and the by-products of nuclear physics have also provided several new agencies whose efficacy is being tried out in the field of radiation therapy. Fast neutrons were shown several years ago to have profound biological action. The usefulness of intense collimated beams of fast neutrons is being studied on more than thirty cases of cancer of the head and neck by Stone and his colleagues.[31] While a number of cases have been treated, it is too early to draw any conclusions from this work. Fast neutrons penetrate tissue to about the same extent as 300-kilovolt x-rays. They produce biological effects which are roughly similar to those of x-rays, but show several points of marked contrast. For example, skin reactions produced by fast neutrons both appear and disappear in a considerably shorter time than is the case for equally intense skin effects produced by x-rays.

Studies of the therapeutic possibilities of slow neutrons were initiated by Kruger and have been continued by him and other workers.[32] It is well known that both boron and lithium capture slow neutrons and that the resulting nuclear reaction liberates energetic alpha-particles. Efforts are being made to localize molecules containing boron or lithium in tissues which it is desired to radiate. Since the probability for the capture of slow neutrons is much greater in the case of boron and lithium than for the other atoms present in the body, the radiation effects would be confined almost exclusively to the region in which the boron or lithium containing molecules had been localized. Difficulties in administering and preventing the diffusion of these materials must be overcome before the method can be used for therapy.

Wherever an artificially radioactive substance can be localized in a tissue which is in need of radiation, really selective interstitial irradiation can be readily administered by the use of very strongly radioactive materials. J. H. Lawrence and his colleagues have shown that phosphorus becomes concentrated in the bone marrow of humans[33] and in the leukemic tissues in mice.[34] Based on this and other evidence, radioactive phosphorus administration has been tried as a possible therapeutic agent in some seventy-five cases of human leukemia. The results in cases of acute leukemia are not encouraging, but in the chronic leukemias further work seems certainly to be justified. Up to the present the results[33] in many cases appear to be at least as good as those obtained by generalized x-radiation of the patient. The administration of radioactive phosphorus can be by mouth, and is certainly much simpler and easier on the patient than the use of whole-body x-radiation.

Some of the machines originally designed for nuclear disintegration have been modified so as to be very effective x-ray generators. The Sloan high frequency resonance transformer has been used for a number of years in two hospitals as a high intensity x-ray generator[35] operating at about one and one-quarter million volts. More recently Trump and Van de Graaff have extended the principles of the Van de Graaff electrostatic generator to produce very compact and efficient supervoltage x-ray generators.[18] By the use of high pressure Freon as an insulating gas, these workers have successfully constructed an x-ray generator which operates continuously at 1.2 million volts and is completely contained in a cylindrical tank two feet in diameter and six feet high. This generator operates at 0.5 milliampere, and produces fifty roentgens per minute at a distance of seventy centimeters, with two millimeters of lead and five millimeters of copper for filtration. A similar generator, to operate above three million volts, is now nearing completion. The first million-volt x-ray generator of the Van de Graaff type has given excellent hospital service for over six years.

These high voltage generators may also be used for the production of intense and homogeneous beams of cathode rays.[36] These cathode rays have not yet been tested for therapy, but they give

every indication of being useful in the radiation of surface or superficial malignancies. The depth of penetration of 1.5-million-volt cathode rays is about eight millimeters in living tissue. Thus the use of cathode rays would permit expenditure of all the radiant energy in a relatively thin layer of surface material. The thickness irradiated can be regulated by adjustment of the cathode-ray voltage. Even with the use of very soft x-rays, say 100 kilovolts, so favorable a distribution of energy near the surface cannot even be approximated.

Physics

At least one completely unambiguous case exists in which applied nuclear physics has directly benefited the parent science of physics, in this case the field of spectroscopy. Wiens and Alvarez have prepared spectroscopically pure discharge-tube sources of the single isotope of mercury of mass 198 by nuclear transmutation.[37] Gold has but one isotope, of mass 197, and captures neutrons to form radioactive gold of mass 198. This isotope has a half-period of 2.7 days and decays into Hg^{198}. By making use of the stray neutrons from a large cyclotron it is possible to prepare tubes containing pure Hg^{198} at a pressure of the order of 10^{-3} millimeter of mercury. As a spectroscopic standard of length this single isotope offers the enormous advantages of complete absence of hyperfine structure and of isotope shift, and because of its high mass possesses very little Doppler broadening.

The Future

As to the future of applied nuclear physics, it is clear that an urgent demand exists for the wider availability of its tools and materials, and of analysts who are well trained in physics and who can work sympathetically and effectively as members of research teams in sciences other than physics. The commercial production of isotopes, both stable and radioactive, is being seriously considered by several large industrial companies. Similarly, high quality detection apparatus is becoming available commercially. And of great importance is the coming new profession of analytical physicist. By analogy with the industrial analytical chemist we can expect an increased demand for analytical physicists possessing the bachelor's degree, and being especially well trained in radioactivity and mass spectroscopy. In addition, a number of truly hybrid Ph.D.'s will be required who can bridge the gap between physics and other scientific fields and whose breadth of knowledge fits them to act as key men in the cooperative research teams of the present and future.

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THE miracles of science, it is true, can be an adjunct of war, but they are not a cause of it. Belligerency is a state of mind, not of matter.

DAVID SARNOFF in "Science and Security"

Separation and Use of Stable Isotopes*†

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Introduction

ABOUT eight years ago Washburn discovered the electrolytic method for the separation of isotopes of hydrogen and this method led to the first successful separation of the isotopes of an element in quantity sufficient for physical and chemical research. The amounts that have been prepared in this way have been truly large considering the difficulty of such separation processes in general. However, this method is so well known and so specialized that no attempt will be made to discuss it in this paper.

Four methods for the separation of isotopes other than hydrogen have been developed in recent years. These are the two Hertz diffusion methods, the thermal diffusion method of Clusius and Dickel, and the distillation and chemical exchange methods. In addition to these, the mass spectrographic method has been used for the separation of minute quantities of material which have been useful in some transmutation reactions, but which can hardly be expected to supply material for general physical and chemical research. It is the objective of this paper to discuss the four separation methods which have been used extensively.

Description of Methods of Separation

Aston[1] very early in the work on the separation of isotopes tried diffusion through porous materials. If this method is to be successful it is necessary that the holes in the porous material be not larger than the mean free path in the gas, and this requires either that the pressures at which diffusion is taking place be low, or that the holes in the porous material be small. Porous porcelain diffusing membranes have been used in such experiments. Hertz[2] introduced the cascade system for carrying out such diffusion, and in this way multiplied the effect of a simple diffuser. His diffusion system is illustrated in Fig. 1. Gas enters one of the units shown enclosed in the broken lines at A, diffuses through the porous tube at R, the diffused material leaving at B, and is pumped to a preceding unit as shown. The heavier material flows as indicated by the arrow to a diffusing unit S, and the lighter fraction flows through C to the pump P_3, while the heavier fraction flows out of this separation unit at D. Hertz has given the formula for the fractionation produced in a single unit as follows:

$$\alpha=\frac{N}{1-N}\Big/\frac{n}{1-n}=\frac{f^{\mu}}{1-(1-f)^{\mu}},\quad \mu=\left(\frac{M_1}{M_2}\right)^{\frac{1}{2}},$$

f is the fraction diffused in each tube, N and n the mole fractions of one constituent in the diffused and residual gas and M_1 and M_2 the molecular weights of the two constituents. It is quite obvious that the over-all fractionation factor will be given by the formula

$$A=\frac{N_h}{1-N_h}\Big/\frac{N_l}{1-N_l}=\left(\frac{f^{\mu}}{1-(1-f)^{\mu}}\right)^{K}, \quad (2)$$

where N_l, (N_h) is the mole fraction of one constituent at the light (heavy) end, and K is the number of units in the diffusion cascade. Various numbers of diffusing units have been arranged into a cascade, one containing as many as 50 such units, and large changes in the ratio of the isotopes produced. The heavy fraction accumulates in the flask at V_s and the light fraction at V_l. Hertz was able to produce a change by a factor of 10 in the ratio of the isotopes of neon at the two ends and the whole apparatus came to a steady state in the course of a matter of hours.

The second Hertz[3] method which several people have investigated depends for the separation on diffusion of a gas through mercury vapor. This arrangement of apparatus is illustrated in Fig. 2, which shows apparatus designed by Sherr.[4] The two units in the cascade shown are not alike, illustrating two units used by him

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with about the same results. Gas entering at D passes between the two cylinders to the region E, where a rapid stream of mercury vapor is maintained. Part of the gas diffuses through the stream of mercury and leaves at C, while the rest remains in the outer chamber and leaves at A. Counter-current flow is maintained as shown by the arrows. In this way cascades of units have been constructed which produce a change in the concentration of isotopes in a gaseous mixture very rapidly. Such cascades have been constructed by Hertz,[3] by Barwich,[6] by Wooldridge[5] and by Sherr,[4] and have been used to concentrate the isotopes of neon, and the isotopes of carbon, nitrogen and oxygen in small amounts. In this way it is possible to produce a few milligrams of, say, the rarer isotope of carbon, per day, in the enriched material. The fractionation factor for the simple process is somewhat larger than the ratio of the square roots of the masses. Sherr, in his work, found that this ratio for the separation of the methanes, for example, was as high as 1.107, whereas the simple process factor calculated from the ratio of the coefficients of diffusion would be 1.03. Though I find it difficult to be certain of this, I strongly suspect that this is due to the fact that the cut taken in the process was small, and hence the rate of production was sacrificed just in the proportion that the fractionation factor is increased. This method of separation is able to produce a few milligrams of C^{13} per day. The apparatus comes to equilibrium very quickly, for the amount of working material throughout the apparatus at a few millimeters pressure will be very small. Hertz reports that he was able to change the ratio of the neon isotopes by a factor of 10 in 45 minutes by similar diffusing units. Diffusion through the gas should be rapid, but the area over which diffusion takes place is small since the tubes shown in the figure are about 1.5 centimeters in diameter, and hence the total area of diffusion is a few cm.^{2} The transport, therefore, cannot be very great. Undoubtedly the speed per unit area in this type of apparatus is much greater than the speed per unit area in the procelain tube type of diffuser.

The Clusius and Dickel[7] thermal diffusion method makes use of the difference in concentration of two gases of different molecular weights at

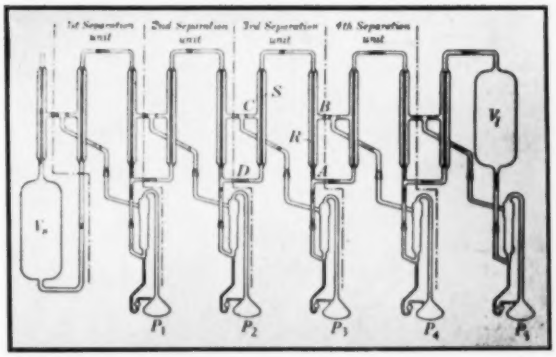

FIG. 1. Hertz' diffusion apparatus for the separation of isotopes.

two surfaces of different temperatures. Clusius and Dickel had the clever idea of mounting the cold and hot surfaces in a perpendicular tube so that convection currents would serve to carry the lighter constituent on the hot surface upward in the tube and the heavier constituent on the cold surface downward in the tube. How this is accomplished can be seen from Fig. 3 taken from a paper by Nier. The spacings of the various tubes are shown on the diagram. By this method it was possible to produce about four or five milligrams of C^{13} per day in a concentration approximately four times that of normal in a 24-hour period. In this case the spacing between the hot and cold surface must be carefully adjusted for the viscosity of the gas, the coefficient of diffusion, and the effect of the gravitational field on producing convection are very intimately related in the theory of this process. Furry, Jones and Onsager[8] have given a complete theory of the thermal diffusion tube which has been proved by Nier to be in close agreement with experiment.

The differential equation for this process has been given by Furry, Jones and Onsager, and is

$$N_1(\mathbf{v}_1-\mathbf{v}) = -D \text{ grad } N_1 + \frac{D_T}{T} \text{ grad } T, \quad (3)$$

in which N_1 is the mole fraction of the one constituent, $\mathbf{v}_1$ the velocity of the first constituent, and $\mathbf{v}$ the convection velocity of the whole mixture. D is the coefficient of self-diffusion for the gas since we may take the coefficients of diffusion of the two constituents as nearly the

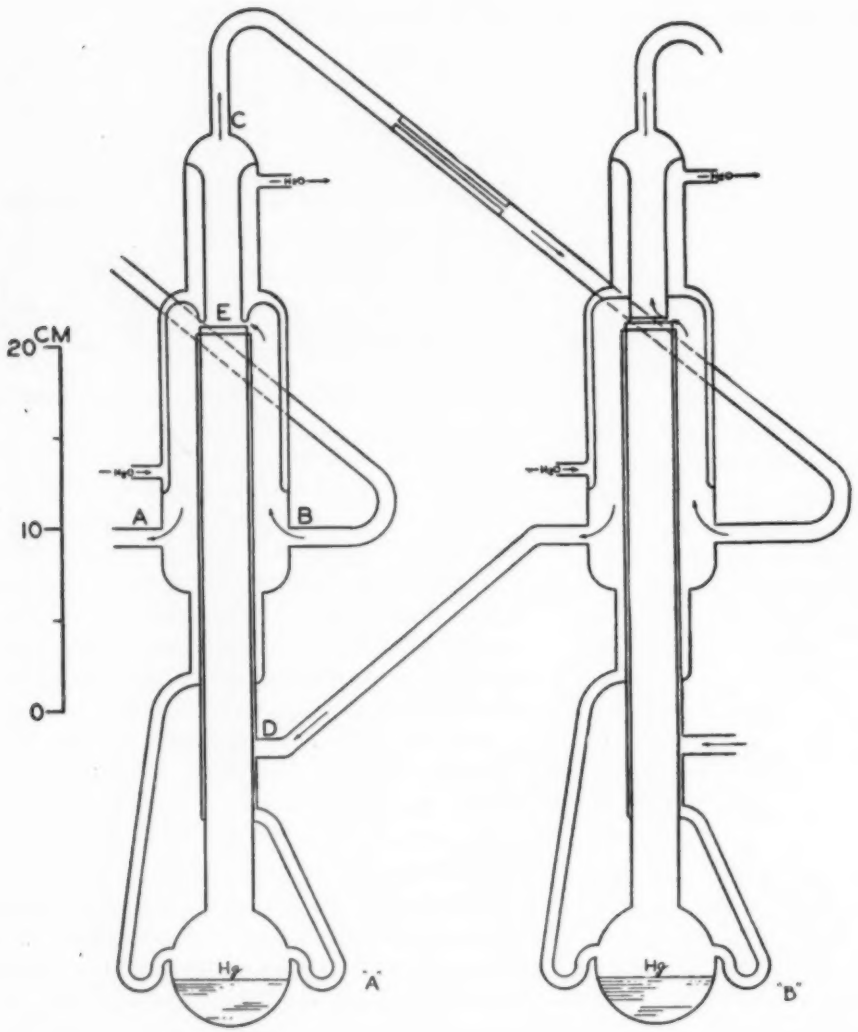

FIG. 2. Sherr's apparatus for the separation of isotopes by the method depending on diffusion of a gas through mercury vapor. (Reproduced from J. Chem. Phys. **6**, 252 (1938). Courtesy of R. Sherr.)

same, and D_T is the coefficient of thermal diffusion. If no convection occurs in the gas, the left-hand side of this equation can be set equal to 0, and the right-hand side can therefore be integrated, if we know the expression for D_T. Theory gives the value for the ratio of D to D_T in the case of hard spheres as

$$\frac{D_T}{D}=\frac{105}{108}\frac{\Delta m}{2m}N_1(1-N_1). \tag{4}$$

The integrated form of this equation then, is

$$\ln\frac{N_1}{1-N_1}\Big/\frac{N_1'}{1-N_1'}=\frac{105}{118}\frac{\Delta m}{2m}\ln\frac{T}{T'}. \tag{5}$$

We shall define as the simple process fractionation factor the ratio of the constituents at the one surface divided by the ratio of constituents at the other, and this expression enables us to calculate this factor. The theoretical value for the ratio of D_T/D as calculated for elastic spheres, is its maximum value. If the inverse fifth-power law of force held between the molecules, the thermal coefficient of diffusion would be zero and hence no separation would be secured. Nier[9] found for the case of methane molecules, that the observed fractionation factor was about one-fourth of that calculated for hard spheres. Furry, Jones and Onsager secured for the operation of such a tube the following formula for the over-all fractionation without forward flow, that

is, with no material removed from the apparatus

$$\frac{N_k}{1-N_k}\Big/\frac{N_l}{1-N_l}=e^{A\Delta l},$$

$$A=\frac{63}{4}\frac{\alpha\eta D}{\rho g w^4}\left(1+\frac{1}{7}\left(\frac{\Delta T}{T}\right)^2+\ldots\right) \qquad (6)$$

(η = coefficient of viscosity, ρ = density, g = gravity constant and w = separation of surfaces) and somewhat more involved expressions if there was forward flow. Nier has found that the theory is very well substantiated using the value for the thermal diffusion coefficient mentioned above. This apparatus is able to produce perhaps as many as 10 milligrams of C^{13} per day in a single such unit and increases the concentration by factors of 6 or 10 depending upon the length of the apparatus.

In this case the speed of the apparatus is determined by the coefficient of diffusion in the gaseous state, since this determines the rapidity with which equilibrium is established between the cold and hot surfaces. The construction of the apparatus must depend upon the coefficient of viscosity of the gas and the force of gravity, since these determine the convection current inside the gas. Moreover, the maximum separation at any point is not secured, for the reason that the streaming in the gas takes place away from the hot and cold surfaces, and hence the maximum simple process factor does not apply in this case.

The chemical exchange methods[10] and distillation methods are so similar that they can be considered together. These methods owe the separation secured to the fact that isotopic compounds of elements of low atomic weight do not have precisely the same physical and chemical properties. There is a difference in the vapor pressures of isotopic liquids, e.g., of the waters and the ammonias. These differences in vapor pressures are about 0.5 percent for the compounds

TABLE I.

Reaction	Equilibrium Constant Calculated	Equilibrium Constant Observed
$N^{15}H_3(g)+N^{14}H_4^+(aq)=N^{14}H_3(g)+N^{15}H_4^+(aq)$	1.033	1.023
$HC^{12}H(g)+C^{13}N^-(aq)=HC^{13}N(g)+C^{12}N^-(aq)$	1.026	1.013
$HCN^{14}(g)+CN^{15-}(aq)=HCN^{15}(g)+CN^{14-}(aq)$	1.003	Slightly less than 1
$S^{34}O_2(g)+HS^{32}O_3^-(aq)=S^{32}O_2(g)+HS^{34}O_3^-(aq)$	——	1.012

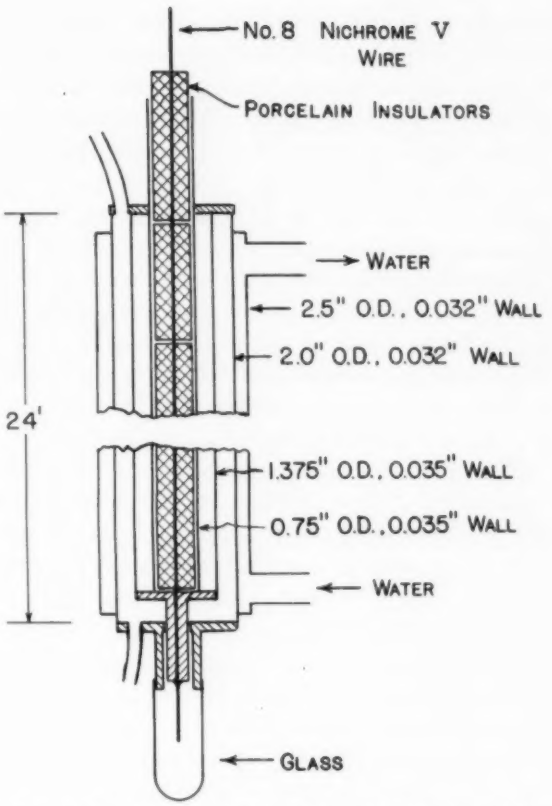

FIG. 3. Cross-sectional view of thermal diffusion column. (Reproduced from Phys. Rev. **57**, 31 (1940). Courtesy of A. O. Nier.)

isotopic in oxygen and nitrogen, so that one is working with very small effects which must be magnified many times. In the case of chemical exchange reactions, it is necessary to secure a gaseous compound which can readily come to equilibrium with a compound in solution. In this case the fractionation factors which can be secured relative to the isotopes of lighter elements are somewhat more favorable than in the case of distillation. Four reactions which have been used for the separation of isotopes are shown in Table I, together with the equilibrium constants calculated on the assumption that the distribution functions for the ions in solution are the same as the distribution functions for the corresponding gaseous molecules. This undoubtedly is not an exact assumption, but seems to be about correct. The observed constants depend upon the operation of the separation apparatus and were nearer to unity in the first two cases than the calculated values, a result to be expected if a limited rate of production is desired. Simple

process factors for these gases are simply the equilibrium constants. It is easy to secure a counter-current flow for the use of these methods, since it is only necessary to allow the liquid phase to flow downward through a tube filled with packing material designed to produce a very large surface, and arrange for the compound in solution to be converted quantitatively at the bottom into the gaseous compound which can then be forced upward through the tube and to arrange for the gaseous compound at the top to be converted to the compound in solution which can then flow back again. In this way a counter-current flow is maintained similar to the other methods.

The apparatus commonly used for this purpose consists of tubes packed with glass helices designed by Fenske.[11] This gives, in many cases, nearly the maximum effect that has been secured by any other method, and, in fact, Fenske's method is a relatively inexpensive one to accomplish this purpose. Other types of packing materials have been devised which are useful for larger units. Figure 4 illustrates the apparatus used by myself and my co-workers for the production of heavy nitrogen and heavy sulfur by this method. It consists of three units in a cascade, the larger one at the left supplying material for the smaller one in the middle, and this again supplying material to the smallest one at the right. Such a cascade of units can be applied to any of the methods which have been discussed. These methods have been used to produce concentrates of N^{15}, C^{13}, O^{18} and S^{34} at a rate of about one gram of the heavy isotope per 24 hours.

The slow process of this method might be either in the liquid phase or the gas phase. Experimentally it is found that a maximum efficiency, with respect to pressure variations, can be secured and Cohen[12] shows that this can be accounted for on the assumption that the slow process is in the gas phase. Such apparatus can be operated on a rather large scale. It should be noted that the simple process factors are of the same order of magnitude as those secured in the various diffusion methods.

A Comparison of Separation Methods

A very important consideration is the amounts of isotopes that are required for the desired

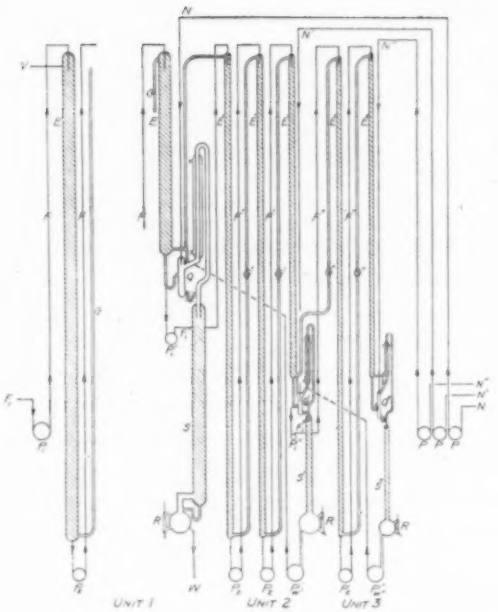

FIG. 4. Apparatus used for the production of heavy nitrogen and heavy sulfur. (Reproduced from H. G. Thode and H. C. Urey, J. Chem. Phys. **7**, 36 (1939).)

experiments. If only small amounts are required the question of cost of apparatus, materials and energy is wholly unimportant; in fact, only in case substantial production is required does the question of cost ever become important. Otherwise, the method to be used depends upon what the experimenter likes to do and can do conveniently with his laboratory facilities.

If one desires only small amounts of material it would seem that the thermal diffusion method is by far the most convenient of any proposed. The consumption of power is high, requiring about $200 worth of electrical energy per gram of C^{13}. This cost might be decreased by using cheaper heating methods, but it seems doubtful if large apparatus can be constructed in single units for this method. If the diffusion unit becomes too large it is very difficult to maintain completely uniform conditions around the diffusion tube, so that parasitic convection currents do not develop. It would appear that Nier's results, securing about 10 milligrams of C^{13} per day, are perhaps what can be secured conveniently by this apparatus, and if larger amounts are desired it would be necessary to build multiple units. Because of the fact that the thermal diffusion method is applicable to many elements, it is of very great usefulness.

The chemical separation methods proceed by a liquid phase flowing over a very large surface of packing material, and by gas flowing through the interstices in a counter-current direction. This method is capable of being developed on a large scale within certain limits. An effective unit probably is one which will transport a few grams of N^{15} or of C^{13} per day. Somewhat larger units may be developed, but difficulties with inhomogeneity of flow through a large tube will become important and have the effect of requiring increased length for a given over-all fractionation factor. Such increased length makes the cost of apparatus greater and will result in a long time being required for equilibrium to be established.

The Hertz diffusion methods are more complicated than the thermal diffusion method, and have about the same production per day for apparatus of the kind that can be conveniently constructed.

The Time of Equilibrium

It is very important to consider the time required for these separation processes to come to a steady state. In the case of any of them the general course of the increase in concentration at one end of the apparatus is a rapid rise of the concentration-time curve followed by a flattening off and an asymptotic approach to the maximum concentration. It is convenient, however, to use a simple formula derived on the assumption that the intial maximum rate of increase of concentration is maintained until maximum concentration is secured. This gives a kind of half-time for the process. This can be derived by calculating the amount of material which will be in the apparatus when the final steady state is reached and equating it to the initial rate of transport multiplied by the time. The distribution of material in any of these methods is given approximately by the formula

$$\frac{N_x}{1-N_x} \Big/ \frac{N_h}{1-N_h} = \alpha^{kx},$$

where N_x and N_h are the mole fractions of one constituent at x and at one end, respectively. The total amount in the apparatus will therefore be

$$\int N_x h dx,$$

where h is the hold-up per unit length of the apparatus and x the distance from one end. The rate at which material is transported from a large reservoir of original material into the apparatus is

$$T = w \frac{N_h(1-N_h)(\alpha-1)}{1+(\alpha-1)N_h}.$$

Carrying out these indicated operations gives us the formula

$$(1-N_h) \ln \frac{1-N_h}{1-N_l} + N_h \ln \frac{N_h}{N_l} = \frac{wN_h(1-N_h)(\alpha-1)}{1+(\alpha-1)N_h} \frac{k \ln \alpha}{h} t,$$

where N_l is the mole fraction at the other end. It should be noted that if one wishes to get a certain over-all fractionation factor in an apparatus it is desirable to keep the hold-up down to a minimum, the rate of flow as great as possible, and to make use of a process that gives the largest possible value for the simple process factor.

The times required for equilibrium are of the order of hours for the Hertz diffusion methods, and of the order of a week or two for the thermal diffusion and the chemical methods. It is necessary, in devising new methods for separating isotopes, to keep this formula or more exact formulae[8, 12] of a similar kind in mind, for it is easy to devise methods that will require centuries to come to equilibrium. In particular, fractionation factors that approach more nearly equal to 1 have a marked effect upon this time of equilibrium. Chemical methods for separating ordinary substances come to equilibrium very rapidly because their fractionation factors are of the order of magnitude of 2 or 3 instead of about 1.02 as for processes considered here.

The Use of Stable Isotopes as Tracers

Because of the great enthusiasm for radioactive tracers which has swept the United States, it is especially important that the advantages and uses of stable isotopic tracers be emphasized. To begin with, it should be noted that a large fraction of chemistry and biochemistry is concerned with the four elements, hydrogen, oxygen, nitrogen and carbon. Hence, though the radio-

active tracers and stable isotopes of other elements than these are very interesting and are useful for much valuable work, the great mass of work must be done with these four elements. Within this region we have the stable deuterium and the radioactive hydrogen as tracers for hydrogen, the stable tracers of oxygen and nitrogen, and the stable tracer C^{13} and the radioactive C^{11} and C^{14}. In the field of other elements we have the stable sulfur tracer and the very good radioactive sulfur tracer. Stable tracers in small amounts can be secured in the case of other elements.

There are several factors, that must be considered in choosing a suitable tracer. In the first place there is the availability of tracer elements; second, the ease with which compounds desired can be synthesized; third, the ease of analysis and the precision of analyses that can be obtained, and, finally, care must be taken to avoid errors due to the chemical dissimilarity of certain isotopes.

Deuterium is an article of commerce and can be had at reasonable prices, and undoubtedly is the cheapest of all isotopic tracers. N^{15} will be produced commercially and will be on the market soon. It seems probable that oxygen, carbon and sulfur will be handled in the same way. The radioactive tracer for hydrogen, tritium, can be had in many laboratories in the United States, where it is produced as a by-product of the bombardment of substances by deuterium. The radioactive C^{11} has such a short lifetime that its use is limited, but C^{14} has a very long lifetime and can be produced as a by-product of the operation of cyclotrons. It is difficult to compare costs of these competitive isotopic tracers. I have estimated the cost of producing a gram of stable C^{13}, N^{15} or S^{34}, as about \$15.00 per gram for labor and chemicals. Further costs, of course, are involved in commercial production. It would seem to me, on the basis of the best estimate that I can get, that such costs are sufficiently low to make stable isotopic tracers serious competitors of the radioactive isotopes in the case of hydrogen and carbon, and only stable tracers are available for oxygen and nitrogen.

In considering the synthesis of compounds it would seem that the element most easily used for tagging a molecule would be hydrogen in the form either of deuterium or the radioactive hydrogen, since this is most easily introduced. However, one must be careful in the case of these two tracers to be sure that the rather marked differences in chemical properties between them and hydrogen will not result in an error in the experimental work. Velocities of reaction involving hydrogen and deuterium often differ by rather large factors—3 to 10—and equilibrium constants for exchange reactions markedly different from simple statistical values also indicate the differences in chemical properties. Such differences will be greater in the case of hydrogen and radio-hydrogen. Also, many hydrogen atoms attached to organic compounds are labile and easily exchange with other compounds, particularly water, in the presence of suitable catalysts.

Next to hydrogen in ease of synthesis would come nitrogen and oxygen, and if one desires a tracer atom for a molecule he will undoubtedly try these next since they are most easily introduced. One must be particularly careful in the case of oxygen to avoid exchange with water, since this is rather common. Finally, it will certainly prove to be most difficult to synthesize compounds containing carbon, but also carbon tracers undoubtedly will have fewer faults of the type mentioned above. As an example, it will undoubtedly be very difficult to synthesize benzene rings containing carbon atoms. Perhaps synthesis of compounds containing carbon atoms could most easily be done by growing whole plants in carbon dioxide containing the tracer carbon. In this way large numbers of chemical compounds interesting to biochemistry could be most easily secured.

Finally, there is the matter of analysis. In the case of the stable tracers it is necessary to oxidize the compounds involved or otherwise reduce them to simple form in order to make analyses. Nitrogen can be most easily analyzed in the form of molecular nitrogen. Oxygen can be most easily analyzed in the form of carbon dioxide. This is most easily secured by bringing ordinary carbon dioxide to equilibrium with water which has been produced by the reduction of organic compounds with hydrogen. In this way O^{18} comes to equilibrium with the water and the analysis of the carbon dioxide gives the concentration of

O^{18} in the water. Carbon can be most easily analyzed in the form of carbon dioxide which is secured by direct combustion of organic compounds. Sulfur is easily analyzed in the form of sulfur dioxide. These analyses can be done with the mass spectrometer which in the hands of Nier and Bleakney has been brought to the form of a very convenient apparatus. Routine analyses with a probable error of about 0.5 percent in the ratio of two isotopes can be made by one who has had a week's acquaintance with such apparatus.

Analyses for the radioactive isotopes which compete with the stable ones are made in various ways. In the case of some they must be secured in gaseous form and must be introduced directly into the counter. This is particularly true in the case of H^3 and C^{14}. While counters are not nearly so expensive as mass spectrometers, there is considerable trouble associated with carrying out these analyses provided the compounds must be reduced to some simple form, as, for example, the form of water, hydrogen or carbon dioxide. The gases must be pure and must be introduced into the counter in exactly the same conditions, time after time, thus necessitating measurements of pressure and control of temperature. It is impossible for me to say anything about the precision of the radioactive methods from my own experience, but it is worth noting that the precision measures for radioactive analyses were never given by any speaker whom I heard at this meeting. In response to definite questions I have been given figures ranging from 3 percent to 10 percent. Such figures do not indicate the precision usually desired in chemical work, though it would seem possible to improve them.

If it is unnecessary to burn organic compounds or otherwise secure the radioactive elements in the form of simple compounds, the radioactive methods of analysis may be much more convenient than the mass spectrometric method. Thus, if a compound containing the tracer can be introduced into the counter directly, much time can be saved in analyses. Further, it should be noted that far greater dilutions can often be secured by the use of radioactive tracers.

My persistent attempts to emphasize the importance of the stable tracers should not be mistaken to mean a disparagement of the radioactive ones, for truly the discovery and development of radioactive atomic species for nearly all the elements of the periodic table is one of the outstanding achievements in physical science in this century. I only wish to emphasize the possible usefulness of the very, very much more modest development of the stable isotopic tracers when there is so much enthusiasm for the radioactive method of attacking these many problems.

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Résumés of Recent Research

Chemical Methods for Increasing the Transparency of Glass Surfaces

"Chemical methods for increasing the transparency of glass surfaces" were discussed by Frank L. Jones and Howard J. Homer in the *Journal of the Optical Society of America* (Volume 31, pages 34–37, January, 1941). The chemical treatment involves the formation of a transparent surface film of low refractive index by selective solution of some of the elements present in the glass. Such removal is possible without damage to the surface polish if the solvent does not dissolve silica. A dilute solution of nitric acid is suitable for leaching most glasses. The rate of film formation is fast for glasses containing large amounts of lead or barium and slow for borosilicate glass. Soda-lime-silica glass reacts so slowly with nitric acid that treatment with this solution is not practical. The rate of film formation approximately doubles for each 10°C rise in temperature. To obtain the maximum transmission and minimum reflection for white light the treatment should be continued until the surface appears purple when examined under water in daylight. Freshly polished surfaces will form a surface layer of uniform thickness and color. Old surfaces usually react unevenly with leaching solutions due to the protective effect of thin films formed accidentally by handling and made acid resistant by dehydration. By following the chemical treatment with a baking operation, the durability of the glass surface can be greatly increased.

Induction Electron Accelerator

The development of a new induction electron accelerator in which it is possible to trap electrons in somewhat circular orbits which miss the injection cathode, and to accelerate these electrons in a doughnut-shaped vacuum tube to an energy of about 2.35 Mev, is expected to facilitate the performance of physics experiments formerly requiring much larger apparatus and great insulation.[1] The instrument, shown in Fig. 1, utilizes a magnetic field oscillating at 600 cycles and reaching a peak value of about 1600 gauss. The accelerator's magnet, surrounding the glass vacuum chamber, is composed of thousands of pieces of iron so that it can be used on alternating current.

FIG. 1.

After the electrons have been thus accelerated to an energy of approximately 2.35 Mev, they are directed against a target. In the present laboratory model of the accelerator, small enough for use on a table, x-radiation somewhat in excess of the radiation from ten millicuries of radium is produced.

[1] This resumé was prepared from reports of a paper, "Induction electron accelerator," given by Donald W. Kerst of the General Electric Company at a recent meeting of the American Physical Society at the University of Chicago; Phys. Rev. **59**, 110A (1941).

For May

Special Issue on Applied X-Rays

***X-Ray Physics and X-Ray Tubes,* by VICTOR HICKS**

***X-Rays in Medicine,* by BENEDICT CASSEN**

***X-Ray Diffraction Methods,* by B. E. WARREN**

***The Evaluation of the Avogadro Number N and the Charge on the Electron e, by X-Rays,* by J. A. BEARDEN**

***Determination of Constitution Diagrams with X-Rays,* by CHARLES S. BARRETT**

Biological Effects of Ionizing Radiations

By G. Failla

Memorial Hospital, New York, New York

NUCLEAR physics is in its early infancy, but, as shown by the great variety of subjects discussed at this Conference, it already exerts an influence on many branches of science and the practical applications thereof. Of these applications none has such a universal appeal as the use of the new tools of nuclear physics in the study and treatment of cancer. In reality, nuclear physics and cancer have been closely associated for about forty years—practically since the discovery of radium—although the term is of very recent origin. But the association now has more points of contact and it is already evident that cancer research, as well as therapy, will greatly benefit from the new developments in nuclear physics. The benefit will come from the study of cancer *per se*, but more important than this, it will be derived from the study of fundamental biological phenomena through the entirely new approach provided by radioactive tracers and stable isotopes. In the ultimate analysis the mystery of cancer is the mystery of life itself.

Nuclear physics is linked to biology in two distinct ways: (1) because ionizing radiations are capable of producing profound changes in the living organism, and (2) because radioactive isotopes provide excellent means for the study of biological processes. This discussion tonight will be limited to the first-mentioned point of contact. A further limitation is imposed by the vastness of the field. Therefore, I shall present only those biological effects of radiation which in my opinion are most characteristic.

It is customary nowadays to class as ionizing radiation any agent which is capable of ionizing matter directly, or indirectly, whether such agent is radiation in the strict sense of the word or a stream of material particles of high kinetic energy. To ionization, which is the common characteristic of all these agents, may be attributed many of the striking properties of ionizing radiations, and in particular the biological effects they produce. Thus, while certain forms of radiation in this class may differ greatly in many respects, they all are capable of producing essentially the same biological effects. Differences do exist but, as far as we know, they are in degree and not in kind, or they are only apparent.

The type of ionization with which we are concerned, is that which results from the passage through matter of electrically charged particles endowed with a sufficiently large amount of kinetic energy. The particles may carry negative or positive charges, may have small or large mass, may receive their quota of energy within the material in which they produce the ionization or externally thereto.

Since the biological effects of radiation are intimately related to ionization, one may expect the simplest relation between dose and effect to exist when the dose is expressed in terms of the ionization produced, during the irradiation, in the proper region of the living organism. This, however, cannot be measured directly and its determination by indirect means is not always a simple matter, especially when all types of ionizing radiation are considered. The subject, though very important, is outside the scope of the present paper, and we shall discuss very briefly only one or two pertinent points. If we wish to correlate radiation dose and biological effect in terms of the ionization produced at a given point in a living organism, what we really mean is to relate the biological change to a certain number of ions produced in a certain time within a given region in the organism. The same number of ions may be produced in the same region and in the same time interval by ionizing radiations of very different types. The important question then is, will the biological change be the same both in kind and degree? In the light of our present knowledge it appears safe to say that in general the biological effect would be the same in kind[1] but not in degree. The differ-

[1] It should be remembered that most of the information we have at present has been obtained by the use of one type of ionizing radiation (x-rays). It is possible, therefore, that differences in kind may be found when neutrons are used more extensively in radio-biology.

ence in degree is attributable to the difference in the spatial distribution of the ions produced by different types of ionizing radiation. In the case of the radiations with which we are concerned here, the ionization is produced almost entirely by the motion of charged particles of high energy in the medium. Therefore, ions are produced only along the paths of these particles, which may be short or long, very tortuous or almost rectilinear, depending on the mass and energy of the particle. Furthermore, the distribution of the ions along the paths may be very different depending on the factors just mentioned. The two extreme cases are those of high speed electrons and recoil nuclei. The tracks of the former are very narrow and the ions are sparsely distributed linearly. The tracks of alpha-particles and recoil nuclei produced by neutrons are relatively wide and densely filled with ions. Thus it is evident that the same total number of ions produced within a given region in a living organism by different types of ionizing radiation, may differ enormously in spatial distribution. What difference this will make in the response of the organism, must depend to a large extent on the nature of the biological change under consideration. Marked differences in the degree of biological damage produced by x-rays and neutrons in some test objects have been reported. While it is true that in these comparisons the equality of the total number of ions produced in the test object by the two types of radiation is uncertain, the difference in the degree of effect, at least in some instances, is entirely beyond this uncertainty. The experimental evidence available at present is too scant to permit generalization, but it would seem that on the whole, radiation which produces ionization with high columnar concentration (alpha-rays, neutrons) is biologically more effective. However, cases in which it is less effective have also been reported.

With this brief discussion of the causative agent we may now turn to the receptor in which the reaction takes place. A living organism consists of one or more cells in a suitable environment. Aside from certain properties common to all, living cells differ enormously in structure, life cycle, and function. The differences have been brought about by evolutionary processes acting through countless generations. In all cases an exquisite adjustment between cell and environment has been attained. Since variations in the environment do occur in nature within certain limits, cells, and aggregates of cells, have developed means to counteract or minimize the influence of such variations on their physiological processes. Thus marine forms can live at temperatures which differ greatly between summer and winter. Warm blooded animals, which require a certain temperature for normal functioning, are provided with means to maintain their body temperature constant in spite of variations in ambient temperature within natural limits. A cell, whether it lives as an isolated entity or is a part of a very complex organism, is endowed with a membrane which permits the passage into the cell of substances necessary to its normal life and excludes others. The mechanism of membrane semipermeability is so delicately adjusted that in some cases it can differentiate between two very similar chemical elements such as sodium and potassium. Thus a living cell is equipped to maintain physical and chemical factors in the cytoplasm with the degree of constancy required for the proper functioning of physiological processes. The nucleus, which resides within the cell, is, therefore, well protected from ordinary disturbances. This is important because not only is it the controlling center of the cell, but it is essential to the self-perpetuation of the cell.

Now all barriers which nature has provided to protect the nucleus, are of no avail against penetrating radiation, such as x-rays, because the disturbance is produced right within the living matter, including the nucleus. It is no wonder, therefore, that ionizing radiations can cause profound biological changes. What changes actually occur depend on many factors, but taking everything into consideration, the magnitude of the dose of radiation is the most important one. It is, of course, obvious that by using a sufficiently high intensity of radiation any living cell or group of cells could be made to absorb enough energy in a short time to raise the living matter to a temperature beyond the tolerance limit. To cause cell death in this way, however, prodigious doses of ionizing radiations would be required. Actually, the lethal dose

even for the most resistant cells is such that no perceptible rise in temperature occurs. In fact the amount of energy involved is extremely small. This is one of the striking characteristics of the biological action of ionizing radiations, to which we shall return later. The most remarkable effect of ionizing radiation, however, is that which produces inheritable chromosomal changes. In this respect ionizing radiation is unique, for it accomplishes with the greatest of ease what had not been done at all artificially before its advent.[2] The new tool has been of inestimable value to the science of genetics. It is appropriate, therefore, to examine this effect of radiation in some detail.

The nucleus of the living cell contains a certain definite number of thread-like structures known as chromosomes, each of characteristic form and size. It has been postulated that the hereditary factors are extremely minute physico-chemical entities, called genes, which occupy definite positions in the chromosomes. In sexually reproduced organisms the fertilized egg has a definite number of *pairs* of chromosomes. One member of each pair is supplied by the egg while the other member is supplied by the spermatozoön. Thus all the genes, except those in the sex-determining chromosomes, occur in pairs, one member of each pair being derived from each parent. When the cell divides, each chromosome and each gene also divide and each daughter cell carries a full complement of pairs of chromosomes and of genes. Hence all nucleated cells of the body of an organism will be alike in this respect and will contain hereditary factors from both parents. The number of genes in the cell must be extremely large, of the order of thousands, to account for all the hereditary physical, physiological, and mental characteristics of the individual.

It is important to remember that hereditary characteristics depend not only on the presence of the genes in the cell nucleus, but also on the positions which they occupy in the chromosomes. Destruction or serious damage of a gene alters the genetic characteristics of the cell. Genetic changes occur also when chromosomes break and the pieces rearrange themselves differently, in which case the positional order of the genes is different. It may also happen that a cell does not receive the full complement of genes because a chromosome or part thereof has been eliminated at the time of division of the mother cell. Or, on the other hand the cell may have more than its due share of chromosomes and genes. When changes of any one of the types just mentioned occur, they are transmitted to all the daughter cells and a *mutation* has occurred,—provided, of course, that the change is not lethal. Now, as pointed out before, all the nucleated cells of an organism carry the same chromosomes with genes in the same characteristic order. Therefore, mutations can occur in any cell of the body. However, it is obvious that if the altered cell is one which does not divide, the change ends with the life of the cell. If the chromosomal alteration occurs in a cell which gives rise to an organ of the body, the organ may be abnormal, but the abnormality ceases with the death of the individual. On the other hand, if the chromosomal change occurs in a germ cell, the alteration is transmitted to all subsequent generations, provided the change is compatible with life and reproduction.

Mutations occur spontaneously in nature, but only rarely. Probably the phenomenon has played a very important part in evolution. If this is true, it is not surprising that the vast majority of mutations give rise to inferior hereditary types; for the present stock probably represents the survival of the single best of the myriads of changes which the hereditary organism has undergone in its past evolution, with respect to the environment to which every individual of the species is subjected. The effect of ionizing radiations is to increase markedly the frequency of mutations which are known to occur in nature. Thus geneticists are now able to make observations in a small fraction of the time that it would take if they had to wait for spontaneous mutations.

The organism which has been used most extensively in the study of genetic changes induced by radiation is the fruit fly, *Drosophila*. It should be noted, however, that the fundamental principles derived from these studies are applicable to all living beings, including man. In every body cell of *Drosophila* there are

[2] More recently genetic changes have been produced by other means, notably heat.

between 3000 and 5000 different genes, which control the physical appearance, physiological processes, behavior, etc., of the individual. Interference with the genes as to number or arrangement may manifest itself, therefore, in innumerable different ways. Interference with certain genes, either in number or position, causes changes which are lethal, and that ends the story. As already alluded to, the great majority of genetic changes, whether occurring spontaneously or brought about by radiation, are either lethal or injurious to the organism. For purposes of study those changes which cause differences in the physical appearance of *Drosophila* have been found most convenient. Genetic changes may be brought about by irradiating males, females, or both. The following experiment quoted by Demerec will serve as an illustration. *Drosophila* males were irradiated with 5000 roentgens and then mated to normal females. About 90 percent of the offspring died before reaching the adult stage, most of them in the early embryo stage. Of the individuals which reached maturity about 40 percent carried chromosomal rearrangements and about 12 percent lethal changes. It seems very likely that an exceedingly small number of them escape some detrimental hereditary change. Compare this with the rate of naturally occurring mutations in *Drosophila* which is given by Zeleny as 28 to 61 per 100,000 flies. Furthermore, the natural rate for *Drosophila* is very much greater than that found in most organisms.

We may now discuss briefly the mechanism whereby genetic changes may be produced by ionizing radiation. We have said that the genes are probably extremely minute physico-chemical entities located in the chromosomes in definite positions. We have also pointed out that in an irradiated tissue ions are produced, and that these ions are distributed along the paths of the ionizing particles. The volume occupied by each ion, or its sphere of influence, is extremely minute. Let us assume that when an ion pair is produced within a gene or within a certain radius therefrom, the gene is put out of commission or altered in some way. The occurrence of such a coincidence is then a matter of chance and the problem is amenable to mathematical treatment. This would also be true if in order to damage or destroy the gene more than one ion pair would have to be produced in the given region within a certain (small) time interval. Similarly, breaks in chromosomes may be accounted for by the production of one or more ion pairs at the point of breakage of the chromosome, or by the crossing of a chromosome by the ionizing particle. This mechanism of the action of radiation in producing genetic changes has found favor with both physicists and geneticists, and there is much indirect experimental evidence to support it. However, its correctness has not been established beyond all doubt.

An enormous amount of work has been done since Muller demonstrated conclusively in 1927 the genetic effects of x-rays. Only an expert can delve successfully into this branch of science at the present time. For our purpose it suffices to recall certain general relationships. Genetic changes have been found to occur in direct proportion to the dose of radiation, over a wide range of dosage. In suitable material chromosomal breaks have been observed following the administration of only a few roentgens. Large doses produce a very high rate of genetic changes as compared to the rate of spontaneous changes. Obviously, the largest dose that can be used is that which enables at least a few individuals of the irradiated population to survive for the length of time required by the experiment. In this case, while the rate is high among the survivors, it is nevertheless low—at most a few percent—when related to the total number of individuals irradiated. (See Demerec's experiment mentioned above.)

The linear relation between dose and genetic effect for a particular case is illustrated in Fig. 1. While the experimental points are rather scattered, the straight line as drawn shows about the best fit that could be expected. It is of interest to examine such a curve at the lower end, corresponding to very small doses, but very little experimental data is available in this region. We have, of course, an experimental point at zero dose, that is, the rate of genetic changes occurring spontaneously in the organism in question. Now, it is known that all living organisms are subjected to ionizing radiations throughout their life, on account of the natural radioactivity of the earth and cosmic rays.

Muller conceived the idea that perhaps spontaneous genetic changes could all be attributed to these ionizing radiations. If this were the case, the natural rate of genetic changes with its appropriate dose of natural ionizing radiation should fit on the extrapolated straight line. Muller and Mott-Smith calculated the dose of such radiation received by an organism during its reproductive life from all known contributory sources, including the potassium ordinarily found in living cells. They found that this dose is entirely too small to make the point fit the straight line. Accordingly, the vast majority of naturally occurring genetic changes must be attributed to causes other than radiation. This conclusion is based on the assumption that the straight line relation between dose and effect holds for very small doses also. If this is not the case, it may well be that radiation from natural sources is responsible for the observed rate of genetic changes. In this case, however, we must

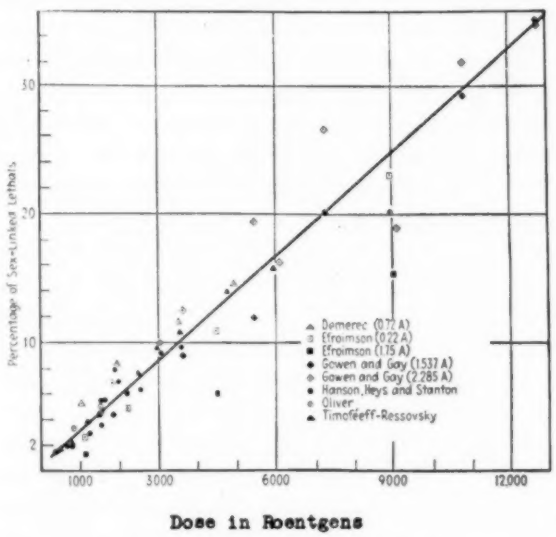

FIG. 1. Percentage of lethals in the X-chromosome of *Drosophila* melanogaster in relation to the dose of radiation.

conclude that *per unit dose* very small amounts of radiation are much more genetically effective than large ones. More work is required to establish which alternative is correct. The matter has important implications in the practical problem of protection against ionizing radiations.

A few other characteristics of the genetic effects of radiation deserve at least brief mention. A certain dose of radiation is equally effective whether it is administered in a short or a long time or in fractions at intervals. There is no recovery in hereditary changes, whether genic or chromosomal. The effect is cumulative over the entire life of a cell. However, in an irradiated tissue with a large population of cells, those which are genetically altered divide more slowly so that they are found in smaller proportion as time goes on, and tend to be eliminated. For the tissue as a whole, therefore, the genetic changes are not cumulative and there is recovery. This is also important in connection with the problem of protection, as indicated by the following data brought out by Demerec: "If a *Drosophila* male is treated with 3000 roentgens, the sperm which was mature at the time of treatment carries about 60 percent of dominant lethals, while the sperm which develops later carries only about 10 percent of dominant lethals. In this case the larger portion of lethal changes were eliminated during two cell divisions which occurred between irradiation and maturity of the sperm."

Perhaps at this point something should be said about dominant and recessive changes. If the radiation effect is on a dominant gene and in a germ cell, the new characteristic of the organism will be present in every one of the offspring and subsequent generations even when mated with normal individuals. If the mutant gene is recessive, the changed characteristic will appear in the offspring only when it occurs in both egg and sperm cell. From the point of view of protection this means that some of the hereditary changes produced in the germ cells of a person exposed to radiation, do not manifest themselves in subsequent generations unless the individual marries some one who harbors similar genetic changes. Since spontaneous genetic changes are very rare the probability of this coincidence is extremely small, but it may become appreciable if both sexes have been exposed to radiation. When such coincidences do occur only one-fourth of the first generation offspring will manifest the altered characteristic.

A discussion of radio-genetic changes before this Conference must include some reference to the influence of wave-length and the type of radiation. The experimental evidence available

so far points to the conclusion that in the case of x-rays and gamma-rays equal ionization doses produce equal effects, irrespective of wavelength. This probably holds true also for high speed electrons and positrons. On the other hand, for equal ionization doses, alpha-rays and recoil nuclei set in motion by neutrons have been found to be, in some instances, much more genetically effective than x-rays. The maximum

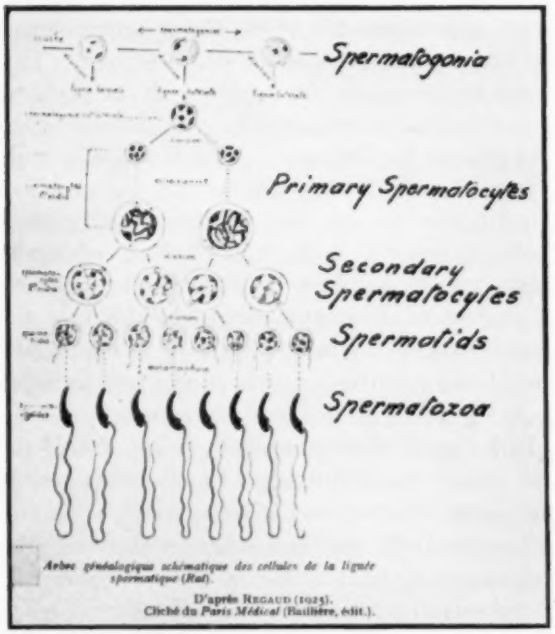

FIG. 2. Evolution of spermatozoa in the rat testis (Regaud).

difference found so far is one to sixteen in favor of neutrons, as reported by Giles. There is, of course, some uncertainty about the measurement of neutron ionization under conditions applicable to biological work, but the reported difference is certainly far beyond the uncertainty in dosage measurements.

From the foregoing discussion it must be evident that ionizing radiations are capable of producing all sorts of biological changes at least as manifestations of genic or chromosomal derangement. However, they can also produce a vast variety of effects which are not necessarily related to genetic disturbances. Under the influence of radiation the living cell receives energy in a very specialized form which is known to induce chemical changes, and for this reason, if for no other, biological changes must ensue, provided the dose is large enough and the time of administration not too long. A great many biological effects of radiation have been described, and it is obviously impossible to cover the subject with any degree of completeness in the allotted time. Therefore, I shall attempt to discuss only a few of these effects, choosing those which in my opinion serve best to illustrate the outstanding characteristics of the action of ionizing radiation on living organisms.

Aside from the production of mutations, already discussed, the most striking characteristic of the biological action of radiation is, perhaps, the delay which occurs between the administration of the radiation and the final manifestation of the change. Thus, while a sunburn appears within a few hours following exposure to sunlight, a similar skin reaction produced by x-rays may not become visible for two or more weeks. Some of the factors which are responsible for the apparent delayed action of ionizing radiations may be brought out best by describing an experiment.

Regaud has made extensive histological studies of the effect of radiation on the testes of the rat. He gives the following (well-known) spermatogenic sequence (see Fig. 2): The *spermatogonia* after a number of divisions and a period of growth, become *primary spermatocytes*. These divide and form the *secondary spermatocytes*, which in turn divide and form the *spermatids*. No further division occurs, but these cells gradually change into *spermatozoa*. Now Regaud and Blanc found by experiment that the spermatogonia are much more sensitive to radiation than all their descendants. Accordingly, it is possible by a suitable choice of dose, to destroy all the spermatogonia without seriously damaging the other cells. Schinz and Slotopolsky have observed cytolysis of the spermatogonia two hours after irradiation, but it takes about four days for all to disappear. On the other hand, the other cells remain and few manifest radiation damage. Subsequent observations show that the life cycles of the remaining cell types continue to be essentially normal. The primary spermatocytes divide into secondary spermatocytes. The process goes on until about the 28th day one finds in the seminiferous tubules only spermatozoa. Finally (between the 28th and 34th day), these

disappear also and the tubules are free of all seminal elements. It is only at this time that the testis can be said to be sterile. Therefore, in this sense, sterility of the male rat does not occur until about one month after the radiation treatment. Depending on the dose, sterility may be permanent or temporary. In the latter case, after a certain time, spermatogonia will reappear in the testis, will pass through the normal transformations, and will finally produce spermatozoa.

One of the important points which may be derived from this experiment is the following: According to Regaud, one month is approximately the normal time which must elapse for the spermatogonia to change into spermatozoa. Therefore, the long time interval between treatment and resultant sterility, is in reality a characteristic of the rat testis and not of the radiation. But, upon further analysis, it is evident that the long interval resulted from the fact that the radiation destroyed the spermatogonia without appreciably injuring the other cells, or materially interfering with the evolution of immature cells into spermatozoa. Accordingly, the truly remarkable thing is that in the same organ, certain cell types can be destroyed by radiation without serious damage to coexisting cells of other types. Whether this characteristic should be attributed to the radiation or to the biological material is largely a matter of point of view. Certainly the high penetrating power of the radiation plays an essential part, since without it the energy necessary to cause the dissolution of the spermatogonia could not be delivered to them without interfering with the other cells. Without going into further details, two important points are illustrated by the foregoing discussion: (1) Radio-biological reactions are characterized in general by a long so-called "latent period." (2) Different types of living cell exhibit different "radio-sensitivities." Attention may well be called again to the fact that the long latent period is more apparent than real, and depends on what end point is chosen for the reaction. For example, mention has already been made of the fact that cytolysis of spermatogonia can be detected two hours after irradiation. Chromosomal changes in suitable material can be seen under the microscope very soon after treatment, but of course, one must wait for the offspring to see what the final result is. It should be remembered too that the "latent period" is also a function of the dose. Complete sterility of a rat has been obtained in seven days by using a large dose of x-rays. The period could be shortened further but very large doses would be necessary, because adult spermatozoa are extremely radio-resistant, at least insofar as motility and ability to fertilize an egg are concerned.

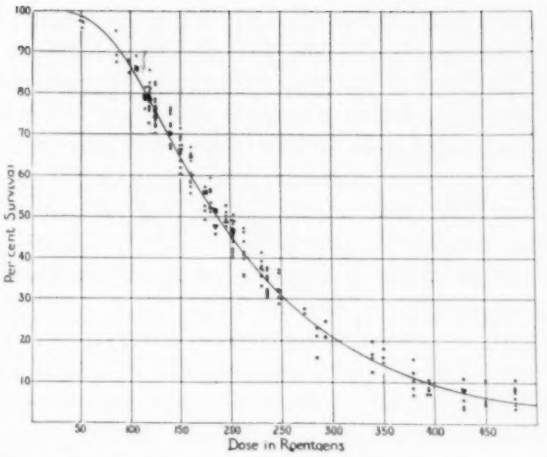

FIG. 3. Survival curve of *Drosophila* eggs treated with x-rays (Packard).

The subject of radio-sensitivity may well be discussed at this point. It has many ramifications and it involves numerous factors. At the outset it is evident that in order to compare the radio-sensitivities of two test objects, one must first choose a particular biological change which is produced in both by radiation, and the degree of this change to be taken as a standard. Death is certainly the most definite end point and it may be produced in all living things by radiation. On this basis all cells and all organisms could be listed (theoretically) in an ascending order of radio-resistance according to the doses of radiation required to kill them. In such an array the range of x-ray doses would probably be from a fraction of one roentgen to one million or more. However, even in this limited sense, the problem is not so simple because, for one thing, there are great variations in radio-sensitivity among different individuals of a given group. To illustrate, we may consider for a moment some typical "survival curves" which will serve also to bring out other important points: Fig. 3

taken from one of Packard's papers shows the survival rates of *Drosophila* eggs when subjected to different doses of x-rays. It will be seen that a few individuals of a large group are killed by doses of less than 50 roentgens whereas some are able to survive doses of 500 roentgens. Furthermore, this curve applies only to eggs of a certain age, when the criterion of death is failure to hatch as larvae. If the same organism, *Drosophila*, is irradiated at different stages in its development, enormous differences in susceptibility are found: Fig. 4, published in 1923 by Mavor, shows this very clearly. (Doses are expressed in arbitrary units since the roentgen had not been adopted at that time. Also the criterion of death is different from Packard's.) The adult fly is roughly 100 times more radio-resistant than the egg. The doses in Mavor's curve are those required to kill 50 percent of the organisms. The variation of susceptibility of adult flies under the conditions of his experiment, is not given but the range must be of the same order of magnitude as in Packard's experiment. Therefore, taking the most sensitive eggs and the most resistant adult flies, the lethal dose may easily differ by a factor of one thousand in the same organism when all stages of development are included.

An increase in radio-resistance with age occurs in general, although there are exceptions, and usually the difference is not so great as shown by Mavor's experiment. (It should be noted in this connection that the greatest jump in resistance takes place during the pupa stage.) In a general way the same thing holds true for individual cells, but in this case another factor comes in. Starting with a fertilized ovum, a multicellular organism is built up by repeated cell divisions. However, much more than this takes place. By the process of "differentiation" certain cells acquire different properties and form the organs of the body. Thus in the adult organism cells differ enormously in structure, physiological function, etc. Some, like germ cells, continue to divide; others, such as brain cells, never divide once they are formed. Those of the former type are referred to as embryonal or undifferentiated, while those at the other extreme are said to be highly differentiated, adult cells. In between these two there are all gradations. The term "young" or "adult" in this connection does not refer to the actual age of a particular cell but to the degree of differentiation. In other words, it refers to the distance in the evolutionary scale that a cell has traveled from the initial germ cell stage. In this sense "old" cells are in general more radio-resistant than "young" ones. There are, however, many exceptions, because of numerous other factors which influence radio-sensitivity.

The most striking exceptions may be found among human tumors. Cancer cells have in common the characteristic of uncontrolled growth, that is, the property of dividing indefinitely, and they do so insofar as conditions permit. In this respect, therefore, they resemble germ cells and should be radio-sensitive. Cancer may develop in any part of the body, but cancer cells are not all alike. Depending on the organ or structure in which the cancer starts, the malignant cell bears the imprint of that tissue of origin. So much so, in fact, that pathologists are able to determine the location of an unsuspected primary tumor by examining a specimen removed from a "metastatic" tumor in some other part of the body. In view of this resemblance

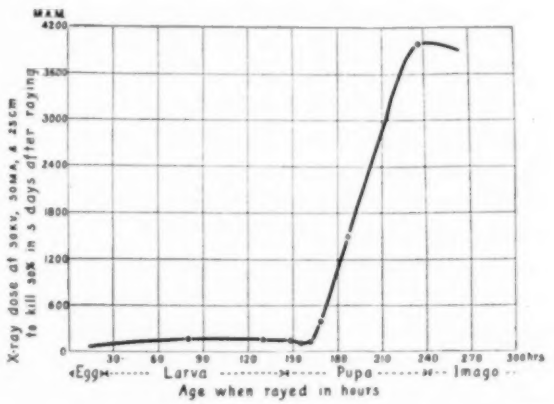

FIG. 4. Radio-resistance of *Drosophila* according to age when treated with x-rays (Mavor).

one might expect that the radio-sensitivity of tumors would be related in a general way to the radio-sensitivity of the tissue of origin. This is true in general. However, considering the embryonal character of the cancer cell (albeit in varying degree), one would expect it to be more radio-sensitive than the tissue in which it

originated. This is true in many cases, but not in many others. The practical significance of this peculiarity cannot be overestimated. In general it determines the success or failure of radiation therapy in a given case. Obviously, when a tumor is considerably more radio-sensitive than the normal tissue in which it grows, it can be destroyed by properly adjusted radiation treatments without undue damage to normal structures. On the other hand, a tumor which is very radio-resistant with respect to adjoining normal tissues cannot be treated successfully by radiation, unless anatomical conditions are particularly favorable. In the case of deep-seated cancers where the radiation (x-rays) must traverse a considerable thickness of normal tissues before reaching the tumor, the problem becomes more difficult.

In view of the obvious practical importance of tumor radio-sensitivity it is justified to dwell on the subject a little longer. In Fig. 5 (from the work of Sugiura) are shown two "survival curves" for Sarcoma 180, a transplantable mouse tumor which is used extensively in cancer research. Some explanation is necessary for the proper interpretation of these curves. A tumor is removed from a mouse and very small fragments of it are inserted under the skin of a number of normal mice. In practically every case (100 percent if the technique is good) the tumor "takes" and in about one week it is approximately 8 mm in diameter. At this time it is irradiated locally with x-rays through a hole in a lead plate. Subsequently the tumor either disappears or kills the animal, depending on the dose. Within a certain range, a definite dose of radiation, administered to the tumors of a large group of mice, causes some tumors to disappear and others to remain. The latter are said to survive the treatment. The tumor survival rate becomes less with increasing dose according to curve *A* in Fig. 5. As in the case of *Drosophila* eggs we may say that there are marked variations in radio-sensitivity among individual tumors of the same histological type (Sarcoma 180). The minimum dose at all capable of inducing tumor regression under these conditions (the "threshold dose") is 500 roentgens, while the minimum dose which is surely effective in all individuals treated is about 2000 roentgens.

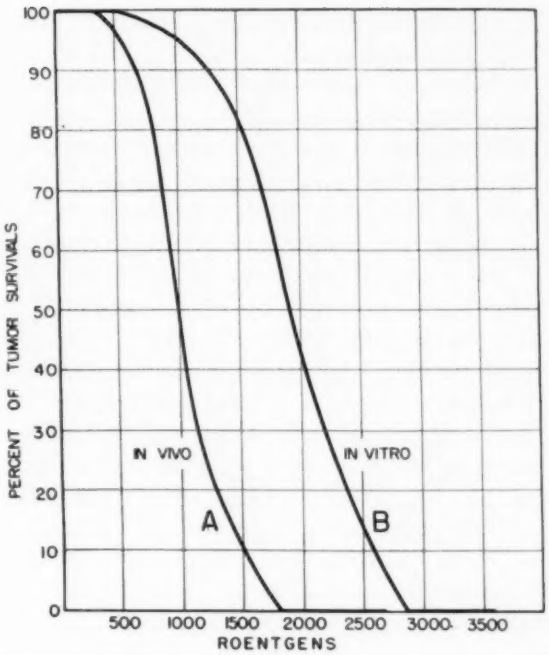

FIG. 5. Survival curves of mouse Sarcoma 180 treated with x-rays *in vivo* and *in vitro* (Sugiura).

In the experiment just described, the tumor fragments were inoculated into normal mice and were allowed to grow actively before they were irradiated. A similar experiment can be performed by irradiating the fragments "*in vitro*" prior to inoculation. Curve B in Fig. 5 shows the results of such an experiment. In this case, of course, the criterion of effect is not tumor regression but failure to "take" and grow. The two phenomena are, perhaps, not exactly comparable. Assuming that in both cases the effect of radiation is a lethal damage produced in the tumor cells, it is strange to find such a marked difference in the doses of radiation required to "destroy" the same percentage of tumors, as shown by the positions of the two curves in Fig. 5. This would indicate that to cause comparable destruction in a tumor irradiated *in vitro*, it takes roughly twice[3] as much radiation as when the tumor is irradiated in the animal. Or, in other words, the tumor irradiated *in vitro* appears to be about twice as resistant as the one irradiated *in vivo*. It is evident that other factors besides the primary action of the radia-

[3] The ratio is approximately 1 to 2 for most of the range of the curves. It becomes about 1 to 1.5 near the end.

tion on the cancer cell, determine the ultimate fate of the tumor.

It might be supposed that the difference is due to the fact that in one case the tumor is irradiated when it is actively growing and in the other case when it is not growing (since it is outside of the body). A very interesting experiment performed by Sugiura shows that this is not the case. If the tumor is irradiated in a living mouse, immediately removed, and fragments thereof inoculated into normal mice, the results are the same as if the tumor had been irradiated *in vitro*. If on the other hand, the tumor is irradiated in the animal and allowed to remain *in situ* for about a week before transplanting to other animals, the results are essentially the same as in the experiment in which the tumors were irradiated *in vivo*. Accordingly, the difference must be due to something which can take place subsequent to the irradiation in an actively growing tumor, and not in a tumor fragment which must first establish itself in the new host. Further discussion of this subject would lead us too far afield, and largely into the realm of speculation. The main thing to remember is that the response of a cell to radiation, when the cell is an active member of a large community, is influenced by the biological conditions which exist in the community. Therefore, one cannot assign a definite degree of radio-sensitivity to a group of cancer cells of a certain histological type as if they were not a part of the tissue, organ, and body in which they live. The reaction of a given tumor to radiation may be said to depend on an "inherent radio-sensitivity" pertaining to the particular cancer cell in question, and to a "derived radio-sensitivity" arising from the biological characteristics of the medium in which the tumor cells happen to be.

A word should be said about the radio-sensitivity of a cell at different times in its life cycle. There is evidence to show that a cell is most sensitive during the process of division, but there is some question as to the exact moment of highest sensitivity. In general (but not always) cells which divide rapidly are more radio-sensitive than those which divide slowly or not at all. Without going into further details, the chief characteristics of the biological response to radiation, insofar as radio-sensitivity is concerned, may be summarized as follows: (1) Cells or organisms which are apparently "identical" at the time of the irradiation are not all affected to the same extent. (2) Cells and organisms vary greatly in radio-sensitivity from one type to another. (3) The radio-sensitivity of any given cell or organism may show very marked variations during its life cycle. (4) Each cell or organism may be said to possess a certain inherent radio-sensitivity (subject to the variations just mentioned, and others) which, however, may be modified considerably by the biological conditions of the medium in which it lives before, during, and following irradiation.

We shall turn our attention now to the question of recovery. A living cell can withstand injury of one sort or another, and can recover from its effects, provided the injury is within certain limits. Injury produced by radiation is no exception to this rule, unless the genetic elements of the cell have been damaged, as pointed out before. The present discussion, therefore, does not apply to genetic changes produced by radiation. A tissue or organism may recover not only because its component cells may recover individually, but also because damaged cells may be replaced by new ones. A tissue, therefore, has greater power of recovery than the component cells, most of which may be destroyed, but are replaced later. It is hardly necessary to add that recovery of a tissue or repair of an injury by the process of cellular multiplication depends largely on the type of tissue under consideration. In the case of the brain, for instance, one cannot expect this kind of recovery, because the cells do not multiply. On the other hand, in skin which is constantly growing to renew the worn out surface layers of cells, one would expect recovery to be marked, and this is actually the case. Let us examine the process briefly, and insofar as present knowledge permits.

The degree of skin damage depends first of all on the dose of radiation. In the human skin, the visible change varies from a slight tanning through various gradations of reddening or "erythema," to complete destruction of the skin. There is a period during which no apparent change is visible on the surface of the skin. The length of

this latent period depends on the dose of radiation and to some extent on its quality. It is obviously difficult to express the degree of reddening of the skin in a quantitative way, especially in patients with different complexions. However, one may determine experimentally with fair accuracy the dose of radiation which produces a just perceptible tanning or reddening on the average patient, that is, the so-called "threshold erythema dose." Much of our information has been obtained by such experiments. The latent period for the threshold erythema is approximately two to four weeks, the shorter period being for rather soft x-rays and the longer for gamma-rays. The threshold erythema doses for different qualities of x-rays are given in Table I (within ±10 percent). It is to be noted that these doses include all radiation which traverses the surface layer of the skin, whether it be direct or scattered radiation. The quality of the radiation is expressed in terms of the half-value layer in aluminum or copper as the case may be.

TABLE I. *Threshold erythema doses for x-rays of different qualities.*

Half-Value Layer Mm	Metal	Dose in Roentgens Including Back Scatter
0.3	Al	120
1.0	Al	270
0.4	Cu	530
0.9	Cu	680
7.0	Cu	800
10.0	Cu	1000

It is probable that this very mild reaction is brought about by an effect of the radiation on the most sensitive cells of the skin, perhaps those in the germinal layer of the epidermis, which normally divide rapidly. The process may be somewhat analogous to that described in the case of the rat testis. The latent period would then represent the time required for the partly damaged cells in or near the germinal layer to go through the normal transformations and reach the surface layer of the epidermis. This is largely speculation, but it is supported for one thing by the observation that with somewhat larger doses the height of the reaction occurs at about the same time as in the case of the threshold erythema. In other words, with larger doses the skin shows a slight reddening sooner, but the maximum degree of reddening is found at approximately the same time interval from the time of treatment. The very marked wave-length dependence of the threshold erythema shown by the figures in the table, has not been explained satisfactorily. By making certain assumptions one can arrive at a tentative explanation, but the subject is too technical to warrant discussion at this time. One thing should be borne in mind, however, namely, that the doses of different qualities of x-rays required to produce the more severe skin reactions common in cancer therapy are not so far apart as in the case of the threshold erythema. In other words, equal doses of x-rays of different qualities tend to produce more nearly comparable skin reactions as the severity of the damage increases.

Going back to the question of recovery, we find that a mild erythema appears, let us say on the average, about three weeks after the administration of a short single treatment. The redness persists for some time but gradually subsides. While there may be some visible difference between irradiated and nonirradiated skin areas in the same part of the body for several weeks, eventually recovery is so nearly complete that no difference in appearance is noticeable. This, of course, is true only when the skin reaction at its height is not too severe. In cancer therapy it is often necessary to administer through normal skin, doses of radiation which destroy the epithelium, leaving a raw surface of characteristic appearance. However, even in this case, almost complete recovery takes place in the course of several weeks. This is so, provided the tissues below the germinal layer of the skin have not been damaged too severely. When the degree of damage of the underlying tissue exceeds a certain limit, healing takes place very slowly,—a matter of months,—and a scar results. Beyond this point spontaneous healing may be impossible, and surgical intervention must be resorted to.

Restoration of the skin surface results, even when the epithelium has been destroyed, because new epidermis is soon formed at the edges of the irradiated field, and gradually covers the irradiated area,—provided the substratum is still healthy. That this condition can exist in tissue

which has been irradiated throughout a considerable depth (at least 2 cm) with practically uniform intensity, is the result of a greater radio-sensitivity of the epidermis with respect to the underlying tissue. The recovery process in this case is one in which damaged cells are replaced by new ones.

There is another type of recovery which may be attributed to a partial recuperation from radiation damage, occurring in the individual cells. The phenomenon may be brought out in the following way: Since the latent period of the erythema reaction is quite long, no appreciable disturbance in the sequence of events should be introduced by administering the dose of radiation in two equal parts separated by intervals of a few hours or even a day. When this is done, however, it is found that no erythema is produced unless the sum of the two doses is considerably larger than the dose administered at one sitting. The longer the interval between the two treatments, the larger is the total dose required to produce the same degree of erythema. For an interval of 24 hours the increase in the threshold erythema dose is approximately 50 percent. For example, with a given quality of x-rays, the threshold erythema dose administered in one short treatment is, let us say, 600 r. To produce the same ultimate skin reaction with two treatments 24 hours apart, each dose must be 450 r, or a total of 900 r. For shorter time intervals the difference is less, and for longer ones it is greater.

For purposes of calculation it is customary to express the degree of recovery of this type as a "loss" of radiation dose over the interval in question. In the example just mentioned, 900 roentgens given in two treatments are equivalent to 600 roentgens given in one treatment. Therefore, of the 450 r administered first, 300 r have been "lost" in the course of 24 hours. Or, in other words, what "remains" of the previous dose, plus the second dose, must be equal to 600 r, since the effect is the same as produced by 600 r given at one sitting. Hence 150 r of the first dose "remain" and 300 r have been "lost." Figure 6 taken from the work of Quimby and MacComb shows the percent "effective" radiation remaining after different intervals, insofar as the threshold erythema reaction is concerned. It will be seen that recovery of the type involved here is very rapid for short intervals of less than one day.

The maximum interval between the two equal treatments used in the experiments of Fig. 6 was 4 days. Since this is already a considerable fraction of the latent period (3 weeks), the reaction is not strictly comparable to that produced by a single short treatment. For one thing changes must be taking place in the skin during this time and the second irradiation therefore acts on skin cells which are not in the same state as during the first treatment. The latent period, of course, is prolonged. However, from a practical point of view, experiments of this type indicate how the effects of intermittent treatments "accumulate" irrespective of the nature of the recovery processes involved.

It is obvious that radiation treatments may be subdivided into more than two parts, and the intervals may be varied in many ways. Or the comparison may be made between a single treatment of short duration and a continuous one administered at lower intensity, lasting a few hours or a few days. The problem, of course, becomes more complex. At any rate, the following general conclusion applies to all such modifications: To produce the same degree of skin damage a larger total dose of radiation is required when the irradiation time is long than when it is short, whether the irradiation is continuous or at intervals.

It is evident from the foregoing that for a given degree of permissible skin damage, much more radiation may be passed through the skin in fractionated doses over a period of time than in a single one. However, the larger amount of radiation reaching a deep-seated tumor may not be more effective in destroying the tumor than it is on the skin. The problem can be settled only by actual trial and long clinical experience. The main factors involved are the relative recovery rates of tumor and adjacent normal tissues, including the skin. Among the innumerable possible combinations of treatment spacings and magnitudes of doses, there should be an optimum one for each particular case. Following the work of Coutard, experience has shown that cancer of the larynx can be treated more successfully by the fractional dose technique than by

the single ("massive") dose method, but opinions differ as to the optimum length of time during which the treatments should be given. The problem is further complicated by large individual variations among patients. A great deal of work remains to be done in this field.

The complexity of the problem of the biological response to ionizing radiation is strikingly illustrated by the following clinical observation. When patients are treated by the fractional method and small daily doses are given for a period of several weeks, the epidermis passes through alternate cycles of destruction and healing, *during the time that radiation is being administered daily*. For instance, in an actual case reported by Friedman, daily doses of 100 roentgens were administered to the skin for 81 days. Erythema commenced on the 8th day and progressed to destruction of the epidermis which reached a peak about the 25th day. Subsequently,

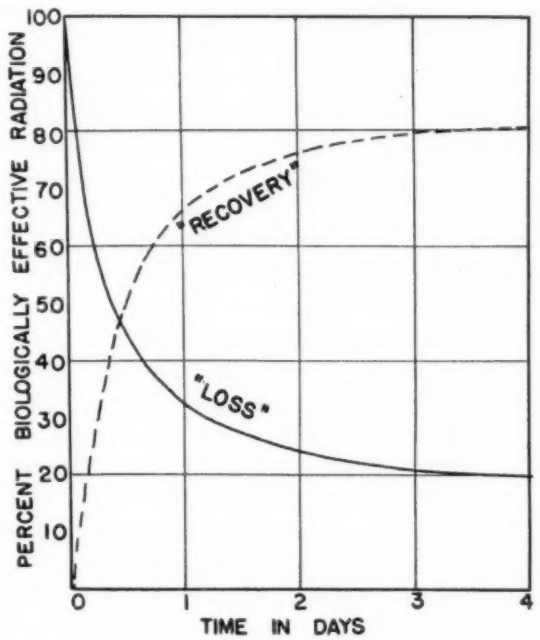

FIG. 6. Loss of effectiveness of radiation in the human skin with respect to time (Quimby and MacComb).

in spite of the daily treatments of 100 r, the skin began to heal and restoration of the destroyed epidermis was complete on the 50th day. At this time the skin showed a mild erythema. Later, skin damage increased again and reached a maximum on approximately the 75th day. Destruction of the epidermis was not so marked at this time as at the previous peak which occurred on the 25th day. The daily treatments were discontinued on the 81st day and the skin showed substantially complete healing on the 87th day. No great importance should be attached to the exact intervals in days between maximum and minimum reactions in the above example. I have chosen equal intervals of 25 days since they are easy to remember and fit the skin reaction curve for this particular case given by Friedman. It is, of course, very difficult to determine such a curve with great accuracy. The positions of the maxima and minima vary from patient to patient and depend on the daily dose. The important point is that human skin is able to recover to a large extent from rather severe damage produced by radiation while more radiation is constantly being administered to the tissue. There is, at present, no satisfactory explanation of this phenomenon. It is, nevertheless, a well-established fact, although not of common occurrence in radiological practice.

Reference has already been made to the small amount of energy involved in biological changes produced by ionizing radiations. In the above example, administration of 100 r per day for 81 days produced rather severe skin damage. One hundred roentgens are equivalent to 8300 ergs per gram of (air or) tissue. A man in repose requires about 1.25×10^{11} ergs per gram of body weight per day, that is, fifteen million times more energy than the skin received per gram during each daily treatment. As a matter of fact the administration of 200 r of soft x-rays *only once* is sufficient to produce a distinct erythema. For the hard x-rays ordinarily used in therapy, the threshold erythema dose (given in a short time) corresponds to 6×10^4 ergs per gram of skin. An individual who can expose his skin to sunlight for half an hour without getting a sunburn, receives 40,000 times more energy per square centimeter.[4] In comparison to the energy required by the body for the maintenance of

[4] Strictly speaking the comparison should be made on the basis of energy absorbed per gram of skin in both cases. As a matter of fact there are objections of one kind or another to all the energy comparisons given here. They are intended simply to convey an idea of the orders of magnitude involved.

normal physiological processes, or the energy received from the sun, a very small amount of energy in the form of radio-ionization is sufficient to cause noticeable biological changes. The erythema reaction has been used for the comparison simply because it can be observed readily with the naked eye. It is not the most sensitive one. A change in the white cell content of the blood can be produced by much smaller doses. The administration of a threshold erythema dose of hard x-rays to the whole body in a short time, would certainly cause death within a few weeks. On the other hand, specialization has produced in the human body cells and organs which respond to extremely minute amounts of energy in certain forms. Thus the ear can perceive a sound when the energy flux is as low as 10^{-9} erg per second per square centimeter. Incidentally, the ear is not injured by a sound one million million times "louder" (10^{3} ergs/sec./cm^2). Curiously enough, the sensitivity of the eye to light (50 quanta per second) is quite comparable to that of the ear for sound in terms of energy, and the range is about the same.

The few examples given here serve to indicate the great variety of the biologic effects which may be produced by ionizing radiations, and the enormous complexity of some of these effects, especially when they take place in a highly organized living system such as the human body. A vast number of biologic effects is known but the actual *modus operandi* of radiation remains obscure and can only be surmised in the simplest cases. The problem becomes incomparably more complicated when exposure to radiation extends over a long period of time, whether continuously or intermittently. Unfortunately such is usually the case in the practical problem of protecting workers from the injurious effects of ionizing radiations. While this subject is outside the scope of the present lecture, a few suggestions may be made here as to indices of biologic damage.

An individual may expose his body to ionizing radiations in the pursuit of his professional activities in a great many different ways. The exposure may be classified as local or general depending on whether a small region or substantially the entire body is irradiated. Whether local or general, the exposure may be of short or long duration, continuous or interrupted. Irrespective of duration the dose may be small or large. The nature, course, and final outcome of the resulting injury depend on all these physical factors. However, it is very important to bear in mind that death may be the final outcome of even an apparently mild local skin injury.

Local overexposure of the skin to ionizing radiation manifests itself first as a reddening of the skin. If a single short exposure is involved the erythema may appear within a short time or perhaps two or three weeks later, depending on the dose received by the skin. The appearance of a marked erythema within the first day is a sure indication that the exposure has been greatly in excess of the skin tolerance limit. Serious complications are to be expected in such a case and the individual should consult a physician[5] immediately. The degree of *skin* damage which will eventually result depends largely on the dose. The final outcome will depend in addition on the penetration of the radiation. If only the superficial layer of the skin is over-irradiated, complete healing will take place and there will be little scarring. On the other hand, if the radiation is very penetrating all the tissues are affected and the prognosis is bad at best. Severe local exposures of this sort are apt to occur in the hand, through accident or sheer recklessness. They end up in deformity and crippling, if not in loss of limb and life.

Local injury may result from topical overexposure to low intensity radiation over a long period of time. How soon skin changes become noticeable depends of course on the intensity of radiation to which the skin is exposed day after day. It may be a question of a few months or a few years. The severity of the injury depends again not only on the cumulative dose but on the penetration of the radiation. If the radiation reaches the vascular system in the underlying tissues, serious complications may result. Circulation is interfered with through constriction or obliteration of blood vessels and fibrosis. Warts or keratoses appear and they may become malignant; or mechanical injury of the skin results in a wound which fails to heal for months and may

[5] Preferably a radiologist who is familiar with such reactions.

eventually lead to cancer. Many radiologists have lost their lives through continued overexposure of their hands to x-rays or radium in the early days of the specialty. A great many others have been incapacitated or have undergone great suffering for many years. The strange thing is that even in recent years there have been far too many cases of severe radiation damage to the hands of radiologists and technicians. Barring accidental exposure there is no excuse for this. Warning signs appear long before the danger point is reached. If the daily dose received by the skin is low enough, no marked erythema may be noticed. In the hand the skin around the nails may become slightly red, dry, and shiny. The nails may show an abnormal curvature (upward or downward), a streaky appearance and unusual brittleness. Assuming that an individual is exposed daily to approximately the same amount of radiation, appearance of these danger signs within a few months is a sure indication that the daily dose received by the fingers is much too high. Continuation of the exposure at the same rate is distinctly dangerous. If exposure of the fingers takes place at a slower rate more time can be allowed for a readjustment of working conditions or change of occupation. However, exposure should not be continued beyond the point at which the skin of the fingers becomes smooth, dry, and leathery and the characteristic ridges disappear. At about this time, also, small wart-like protuberances may be present. At these points the skin grows rapidly and the resultant local thickening makes the region very sensitive to pressure, and causes considerable discomfort.

It should be borne in mind that the skin of different individuals reacts differently and that the danger signs mentioned above may show considerable variations in time of manifestation and appearance, under similar conditions of exposure. However, there is no true idiosyncrasy to ionizing radiation and one need not fear that a dose which is perfectly safe for one adult individual will cause very severe injury to another. The range of skin radio-sensitivity among different individuals is not known, but if I were to hazard a guess, I would say that it is not much greater than twofold. That is, a dose which causes no appreciable skin damage to one healthy person will not cause severe skin injury to another, and one-half of this dose would probably be tolerated equally well by the skin of the sensitive individual.[6] Of course, it is obvious that if the dose is very large, so that a radio-resistant skin may barely be able to recover, the same dose may cause irreparable damage to a radio-sensitive skin.

Fatalities resulting from local overexposure are due to the development of cancer in the over-irradiated region. This possibility should always be borne in mind since it has occurred in numerous cases. Usually an open sore appears in the devitalized tissue, gets infected, and refuses to heal for months in spite of all medical care. When, unfortunately, both the patient and the doctor are reluctant to take radical measures, such as amputation of a finger, cancer develops. In the meantime the tumor may metastasize to other parts of the body and it is then too late to save the life of the patient.

In the foregoing discussion it has been assumed that the overexposure takes place only in a localized region such as the hand. However, when working in the neighborhood of sources of highly penetrating radiation such as gamma-rays and neutrons, freedom from local effects is no index of safety. In this case the whole body may come under the influence of the radiation. Here again the exposure may be of short or long duration irrespective of the dose. Body doses of less than 100 roentgens of x-rays administered within a few days are sometimes given to leukemic patients. It is not known whether the same dose would be safe for a normal individual. However, marked changes would certainly occur, as indeed they do in these patients. It is safe to assume that a body dose of this order of magnitude would be injurious to a human being. It is impossible to say at this time what is the maximum body dose of radiation administered within a few days that man can tolerate without permanent eventual injury of some sort. Our views on this subject are apt to undergo considerable revision as more sensitive methods of detecting radiation changes are developed. Thus recently it has been discovered that body doses of only a few roentgens

[6] There are considerable variations in the radio-sensitivity of different skin areas of the same individual. The most sensitive areas are those which normally are moist, warm, and unexposed, e.g., under the axilla. Therefore, the same skin area should be considered for comparison of individual variations.

of x-rays produce marked changes in the organic acid soluble phosphate compounds of the blood cells in leukemic patients. The same dose does not produce detectable blood count changes. There is little information, also, as to what constitutes a lethal body dose for man when the radiation is administered at one sitting or within a few days. The closest estimate I can make is 500 roentgens.

When the whole body is irradiated the most radio-sensitive tissues or organs, of course, are affected most readily. However, whether we detect the change or not depends among other things on the physiological part which the tissue or organ in question plays in the organism and on the available means of detection. The blood-forming organs of the body are very radio-sensitive and changes in them can be detected readily by a rather simple examination of a very small quantity of blood. Thus the "blood count" constitutes a simple practical index of body exposure to ionizing radiation. It is important to note in this connection that the blood count is influenced by numerous factors including the technique employed in making it. Large normal variations occur from one individual to another and in the same person from time to time, particularly with respect to meals. Also, certain diseases influence the blood count. Accordingly the blood count as an index of constitutional radiation effect must be used with great discretion. (More details will be given presently.) The reproductive organs (ovary and testis) are also radio-sensitive. Means of detecting early changes therein, however, are not practical. Temporary or permanent sterility may be produced by radiation applied locally or throughout the body.[7] The sterilizing dose of x-rays locally applied at one sitting is of the order of 300 to 500 roentgens for both men and women. The differential between temporary and permanent sterility is rather small. The nervous system including the brain is—fortunately—very resistant to radiation. The retina is also very resistant, but cloudiness of the lens and blindness may be produced by fairly large therapeutic doses of x-rays.

[7] Little is known about the latter except in some cases of whole body exposure over a period of years (x-ray or radium technicians) and in such cases, other disturbances become evident first.

Short but large dose exposure of the whole body to ionizing radiations is unlikely under present conditions. On the other hand exposure to low intensity radiation for short or long periods is a common occurrence. Experience with x-rays and radium has shown that if the daily dose received by the human body does not exceed 0.1 roentgen per day, no apparent ill effects result, at least over a period of several years. Many x-ray and radium workers have died of anemia and some of leukemia attributable to continued overexposure, but nothing is known about the radiation dose they received. A larger number must have died prematurely because the effects of radiation made them susceptible to other diseases and reduced their vitality. It is a relatively simple matter to make measurements of the radiation in work rooms in the case of x-rays and radium. Steps can then be taken to keep the exposure of personnel within 0.1 r per day either by protective barriers[8] or by limiting the working hours—preferably by the former. In the case of neutrons some uncertainty exists as to the measurement of the dose and its biological effectiveness on the human body. Accordingly it is wise to err on the side of safety.

Human nature being as it is, the provision of the necessary protective measures and instructions does not stop most workers from exposing themselves to radiation of higher intensity than the adopted tolerance limit, for one reason or another. It is extremely desirable, therefore, to make use of some biological test to detect damage before it is too late. No completely satisfactory test of this type has been found thus far but periodic blood counts, properly made, are very useful. For this purpose complete blood counts should be made regularly once a month, at the same time of the day (2 hours after breakfast), by the same technician, using the same procedure. The findings should be interpreted by a competent hematologist.

The importance of making the blood counts at regular intervals cannot be overestimated. Owing

[8] It is urged that everyone working with ionizing radiations read the two booklets on x-ray and radium protection issued by the National Bureau of Standards, Handbooks 20 and 23. These can be obtained from the Superintendent of Documents, Government Printing Office, Washington, D.C., at a nominal price.

to large fluctuations which occur normally or for reasons other than exposure to radiation, a single blood count is practically meaningless. It is best to obtain blood counts of a person planning to undertake work with ionizing radiations two or three months in advance, in order to establish a norm for the individual. When this is impossible a blood count should be taken before the man assumes his new duties. Incidentally, if this blood count is abnormal and the reason for the abnormality is obscure, the individual should not be employed. In order to illustrate the practical use made of blood counts in our radium laboratory, the data pertaining to one technician during the term of employment are given in Table II. The notation is readily understood by hematologists. As far as the physicist is concerned it may be said briefly that in column 2 is given a color index of the blood in arbitrary units. In columns 3 and 4 are given, respectively, the actual numbers of red and white cells per cubic millimeter of blood. In columns 5 to 10 are given the percentages of the different types of white cells present in the total white count of column 4. The first noticeable effect of radiation is a drop in the white count. Of the white cells the most important ones from the present point of view, are the polymorphonuclear ones (column 5) which bear the main burden of fighting infections. Therefore, columns 4 and 5 should be watched carefully for the detection of overexposure to radiation. Furthermore, the percentages in column 5 (polymorphonuclear) should always be higher than those in column 7 (small lymphocytes). All the variations shown in the table occur in normal individuals not exposed to radiation. However, the general trend of the white count is definitely downward, and on the fifteenth month the differential count shows a reversal, that is, the percentage of small lymphocytes (52) is larger than the percentage of polymorphonuclear cells (46). At this time the man was advised to change his occupation. In the course of the next two months, while still handling radium, his blood picture improved markedly, but nevertheless he was urged to leave. Incidentally it may be added that we make it a practice to let the technicians see the blood counts of all the personnel, and they are aware of the changes which occur.

TABLE II. *Monthly blood counts of a radium technician.*

1	2	3	4	5	6	7	8	9	10
MONTH	HAE.	RED CELLS PER MM³	WHITE CELLS PER MM³	POLYS %	L.L. %	S.L. %	TRANS. %	EOS. %	BAS %
0	85	4,480,000	11,200	47	7	35	10	1	
1	85	4,544,000	8100	52	2	38	8		
2	90	4,544,000	6800	62	3	25	5	5	
3	90	4,512,000	6100	59	0	35	4	2	
4	95	4,608,000	6400	57	3	33	7		
5	95	4,752,000	6400	52	3	32	10	3	
6	85	4,504,000	5800	60	3	33	4		
7	90	4,504,000	7900	47	3	40	8	1	1
8	90	4,604,000	7300	62	2	30	6		
9	95	4,736,000	5200	56	0	38	6		
10	95	4,704,000	7400	62	0	30	8		
11	95	4,704,000	8900	63	3	25	6	1	2
12	95	4,872,000	6100	58	5	30	7		
13	95	4,960,000	6200	73	–	24	1	–	–
14	90	4,768,000	4400	56	4	36	3	1	–
15	85	4,640,000	5000	46	1	52	–	–	1
16	90	4,544,000	5000	61	4	30	5	–	–
17	85	4,384,000	9000	70	–	27	2	1	–
		Blood Count of a Rejected Applicant							
3/9/38	80	4,032,000	3800	40	5	50	3	2	

At the bottom of the table is given the blood count of an applicant who was rejected. The man had never worked with ionizing radiation and felt "perfectly well."

This brief discussion of some phases of the protection problem emphasizes for one thing, the almost complete lack of quantitative data bearing on the subject. The numerous injuries and deaths which have occurred help us very little in this respect. It is too much to hope that there will be no injuries and fatalities in the future. Every effort should be made, particularly by those in charge of radiation laboratories, not only to provide protective means and instruction, but also to make measurements and keep records of the amounts of radiation to which workers are exposed, in order that some day we may have adequate information to prevent injuries without unduly limiting the activities of enthusiastic workers. Among the "martyrs of science" there have been some—and there always will be—who have been simply foolhardy. It is to be hoped that there will be fewer and fewer in the future and that the suffering they go through will benefit others.

Abstracts

from the

Conference on Applied Nuclear Physics

Cambridge, Massachusetts

October 28–November 2, 1940

A GENERAL Conference on Applied Nuclear Physics, sponsored by the American Institute of Physics in cooperation with the Massachusetts Institute of Technology, was conducted during the week of October 28–November 2, 1940, at the Massachusetts Institute of Technology, Cambridge, Massachusetts. The rapidly increasing number of applications of methods and apparatus characteristic of nuclear physics in the fields of biology, radiology, chemistry, geology, and industrial physics has long emphasized the usefulness of a joint conference between physicists and their colleagues in other fields of science.

The purposes of the Conference were to bring together investigators who may be widely separated geographically, and to provide a forum for assembling and correlating present knowledge and difficulties, and for directing attention toward fundamental lines of research which should be the subject of future investigations.

The week's activities were divided into separate sessions on applications to biology, chemistry, radiology, metallurgy, geology, and to general sessions relating to the production and use of radioactive and stable isotopes, and the protection of workers from radiation.

The individual sessions were extremely well attended, and the total number registered approximated 600 persons.

The Committee in Charge of the Program was as follows: Robley D. Evans, Chairman, Massachusetts Institute of Technology; Elmer Hutchisson, Secretary, University of Pittsburgh; Henry A. Barton, American Institute of Physics; Edw. U. Condon, Westinghouse Electric and Manufacturing Company; Lee A. DuBridge, University of Rochester; G. Failla, Memorial Hospital, New York; Clark Goodman, Massachusetts Institute of Technology; Ernest O. Lawrence, University of California; and Harold C. Urey, Columbia University.

The order of the abstracts has been somewhat changed from that in the original program; hence the numbering of the abstracts which follow is not consecutive. Instead, the papers have been classified according to the fields in which the work occurs.

Geology I

Techniques and Standards in Terrestrial Radioactivity Measurements

Chairman: DR. LYMAN J. BRIGGS, *National Bureau of Standards*

1. The Rate of Emission of α-Particles from Uranium and the Relative Activity of Actinouranium. ALOIS F. KOVARIK AND NORMAN I. ADAMS, JR., *Sloane Physics Laboratory, Yale University, New Haven, Connecticut.*

In *The Physical Review* of 1932[1] we published determination of the rate of emission of α-particles from uranium. During similar experiments with thorium, the apparatus was improved to give a greater resolution of close counts of α-particles. Subsequent observations on uranium gave slightly greater rate of emission than the original experiments. The same two specimens used in 1932 and two new specimens of U_3O_8 were used in the experiments. The weighted mean from all experiments involving about 10^6 counted α-particles gives 25.010×10^3 α-particles per second per gram of uranium, i.e., for U I, U II and actinouranium. The 1932 value is 24.770×10^3. The uranium used was pure U_3O_8 prepared by the late B. B. Boltwood.

Attempts have been made to obtain relative activity of actinouranium, in this material, by a method similar to the "step" method used in the study of thorium and its

products.[2] It has been found that such a method is applicable, but with the apparatus used the results were affected by changes of atmospheric pressure so that the desired accuracy has not yet been obtained. However, the results show that the ratio of the activity of actinouranium to that of U I is of the order of 5 percent. More accurate determinations are in progress.

[1] Phys. Rev. **40**, 718–726 (1932).
[2] Phys. Rev. **54**, 413–421 (1938).

2. The Certification of Radioactive Standards. L. F. CURTISS, Physicist, *National Bureau of Standards, Washington, D. C.*

The National Bureau of Standards is cooperating with a Committee of the National Research Council on standards of radioactivity in a program intended to make available standards which will be useful in determining the radium and thorium content of minerals and ores, in the study of radium poisoning, and in the field of artificial radioactivity.

Types of standards which have been considered to date are as follows: (1) Radium standards containing 10^{-9} and 10^{-11} g of radium, suitable as sources of known amounts of radon. (2) Radium standards containing from 0.1 to 100 $\times 10^{-6}$ g of radium, suitable as gamma-ray standards. (3) Rock samples of known origin which have been analyzed for radium and thorium content as well as chemical and mineral constitution. (4) Thorium standards containing suitable amounts of thorium as sources for known amounts of thoron. (5) Beta-ray standards consisting of electrolytic deposits of Ra D on platinum.

The general procedure for preparing the radium standards is well known. It consists simply in dissolving a radium salt of known content and, by dilution, obtaining solutions so that a given volume will contain the desired amount of radium. Precautions must be taken to insure that the radium stays in solution throughout the process.

This paper describes the procedure which has been followed at the National Bureau of Standards in preparing two series of standard radium solutions, one to be used as radon standards and the other as gamma-ray standards. The radon standards consist of 100 ml of solution in sealed Pyrex flasks, one group containing 10^{-9} g of radium and the other 10^{-11} g of radium. The gamma-ray series consist of sealed Pyrex ampoules holding 5 ml of solution with the following radium contents: 0.1, 0.2, 0.5, 1, 2, 5, 10, 20, 50 and 100×10^{-6} g. The 0.2, 2 and 20μ g ampoules are available in pairs so that complete sets of 13 ampoules are available.

Certification of these radium standards is based upon the work of Madame Curie and later of Hönigschmid, who prepared carefully purified and weighed samples of radium and sealed them in glass tubes to serve as gamma-ray standards. These are the primary standards by which the radium content of preparations for medical purposes are usually determined, in terms of their gamma-radiation.

For the preparation of the standard solutions radium bromide was used. The sample available was found to contain 16.394 ± 0.005 mg of radium by comparisons with the National Primary Standard. The value of this standard is certified by the International Radium Commission to 0.5 percent. Therefore, in preparing the solution, methods of dilution and pipetting were adopted which would be certain to introduce no errors greater than this percentage. The resultant standard solutions, after suitable checks on uniformity, may therefore be certified directly in relation to the National Primary Standard.

The radium content of the rock samples is determined by the emanation method, using standard radium solutions for comparison. The measurements for certified standard samples are complicated by a number of factors. Therefore, the committee has decided to submit samples of rocks to at least two laboratories equipped to make such determinations and to base the values in the certificates on the results of these measurements in addition to those made at the National Bureau of Standards. The Massachusetts Institute of Technology and the Geophysical Laboratory of the Carnegie Institution are cooperating in these measurements.

The work on thorium standards and beta-ray standards has not progressed to the point where methods of certification can be discussed.

3. Measurement of Terrestrial Radioactivities. ROBLEY D. EVANS, *Department of Physics, Massachusetts Institute of Technology, Cambridge, Massachusetts.*

For uranium or radium analyses, radon can be separated from rock samples either by the carbonate fusion or the direct fusion furnace. Ionization chamber and electrometer techniques are satisfactory for the measurement of 10^{-12} curie or more of radon, while recording α-ray pulse counters are preferable for weaker samples. The actinium series can also be evaluated from radon measurements on rocks, because of the constant value of the actinium and radium series activity-ratio. For thorium analyses on rocks, chemical separation of ThX provides a parent solution from which the short-lived gas, thoron, can be liberated and flowed continuously through an ionization chamber. Recording α-ray pulse counters again offer the highest sensitivity for detection. Frequent recalibration, using accurate radioactive standards having about the same activity as the samples being analyzed, should be made on all detection apparatus. The National Research Council's Committee on Standards of Radioactivity is continuing to develop new standards of all types. Standard radium solutions, and accurately analyzed standard samples of the principal types of rocks are now available for distribution by the National Bureau of Standards. Standard thorium solutions are in preparation. Results obtained in various laboratories on identical rock samples have now been compared directly by exchange of samples. This international interchecking program has been in progress for about four years, and has brought about substantial improvements in analytical techniques and in the proper use of standards. Much of the data on terrestrial radioactivity, especially in the older literature, requires revision. Determination of the geologic age of an igneous rock primarily involves the measurement of the total helium content and the total rate of production of helium (rate of emission of α-particles)

per gram of specimen. The latter can be calculated for the U, Th, and Ac series from the radon and thoron content. A direct physical method, independent of standards, decay constants, and possible samarium interference, is provided by counting the α-rays emitted from very thin layers of rock sample. This requires α-ray pulse counting apparatus having a very low background. The U, Ac, and Th content of a rock sample can be computed from a comparison of the total α-ray count and a separate radon analysis of the same material. The marked inhomogeneities which occur in some rocks must be evaluated by repeat analyses on the same material. Gamma-rays can be measured by discharge counters if rock samples of about a kilogram or more are available. Such observations represent the combined effects of potassium and of all members of the U, Th, and Ac series. Gamma-ray surveys of oil well drill holes have become a significant new geophysical tool, especially in locating stratigraphic variations. The mean radioactivity of the different rock types is needed for calculations on the earth's internal heat. Mean values of radium content, in 10^{-12} g Ra per g rock, and the ratio of thorium to uranium concentration, for specimens analyzed recently, are as follows. Radium: 1.7 ± 0.2 for 26 acidic rocks; 0.51 ± 0.05 for 7 intermediate rocks; 0.34 ± 0.03 for 41 basic rocks; 0.70 ± 0.12 for 13 sedimentary rocks. Ratio of thorium to uranium: 4.3 for 16 acidic rocks; 2.6 for 6 intermediate rocks; 4.0 for 35 basic rocks.

4. Requirements for a Primary Thorium Standard and Progress in Its Preparation. JOHN PUTNAM MARBLE, *Division of Geology and Geography, National Research Council, Washington, D. C.*

No primary standard for the thorium series exists, so far as is known. Thorium preparations and radioactive measurements in the thorium series have usually been checked against a sample of a mineral of known thorium content. Different workers have used different source materials.

An adequate standard should, we find, consist of a preparation of a thorium salt, made from a mineral whose thorium and uranium content is known, and from which the radium (and its congeners) have been quantitatively separated on a known date. This will enable the correction curve for the growth of radium from the ionium present, and for the subsequent members of the uranium series, to start from a definite zero point, and thus increase the accuracy of the thorium activity measurements.

Preliminary work by Kovarik and Marble, aided by others, has indicated the type of mineral most desirable for use; the practical limits of chemical analysis; the method of preparation to be followed; the means by which reagents of adequate radioactive purity may be prepared; and the difficulties involved in the quantitative separation of radium as of a given date.

Geology II

Geochemical Applications of Radioactivity

Chairman: DR. S. C. LIND, *University of Minnesota*

8. Radioactivity and Geochemistry. ROGER C. WELLS, *U. S. Geological Survey, Washington, D. C.*

Thorium is found in monazite and thorite, which occur in pegmatites, and in some columbo-tantalites. It has also been found in augite syenite. Uranium is found in granitic rocks as uraninite, and also in samarskite, and as the phosphates autunite and torbernite and in several other similar minerals. Carnotite occurs in sedimentary sandstones. For a semiquantitative estimate of the abundance in the crust of the earth of these two radioactive elements (which seem to have a fairly definite abundance ratio to each other) it is necessary to find some common element to which they are related in abundance.

Such an element is potassium (which is also slightly radioactive), and the abundance of potassium in different kinds of rocks is definitely related to the density of the rocks. Studies of the velocity of earthquake waves and of isostacy enable us to arrive at provisional conclusions concerning the density-altitude gradient in the earth and therefore offer a means of estimating the abundance of thorium and uranium in the outer ten-mile crust at least.

Following Williamson and Adams the writer assumes the existence of a basaltic substratum of density 3.3 at a depth of about 37 miles below sea level. Sub-oceanic rocks are about 0.14 more dense than continental rocks on the average. Surface continental rocks have a density of about 2.76 and therefore sub-oceanic rocks must have a corresponding density of 2.90. Taking account of the relative areas of continents (including continental shelves) and seas the average surface density is about 2.85. With these figures as starting-points it is possible to compute three different figures for the abundance of thorium and uranium, assuming that: (1) the composition of rocks continues essentially unchanged from the surface to the level of equal pressure (about 37 miles); (2) the density gradient rises uniformly from the surface to the depth of compensation; and (3) as it is not thought possible for the average density of this layer to exceed 3.1 the other possibility is the density gradient rises rather rapidly to about 3.05 and then continues almost unchanged to a depth of about 29 miles, whence it rises to 3.3 at 37 miles.

With these density gradients it is possible to make an estimate of the abundance of thorium and uranium in the ten-mile crust. The effect of sedimentary rocks and the ocean is only a minor correction.

The first method of calculation gives a maximum, the second a reasonable mean, and the third a minimum figure for the content of radioactive elements. According to the first method there is no change in the radioactive content down to 10 miles below sea level. This conclusion is not supported by the known tendency of rocks to segregate by gravity and hence it seems more likely that density increases at least somewhat even in the "granitic" layer. The second method yields a decrease of about 42 percent in the radioactive content in a distance of ten miles. The third method yields a rather improbable decrease of 50 percent in the same distance.

9. Radioactivity and Oceanography. C. S. PIGGOT, *Carnegie Institution of Washington, Washington, D. C.*

The radioactive relations in the ocean and its sediments are complex in comparison with the simple relations for the igneous and sedimentary rocks that form the continents. This is because neither in the ocean nor in the upper layers of the ocean bottom are elements such as uranium, ionium and radium in radioactive equilibrium. In discussing radioactivity and oceanography the dimension of time is therefore of prime importance. The sediments underlying the deeper portions of the ocean provide suitable material, correlated with this dimension, for studying the growth and decay of these elements. Such studies have established the distribution of the radioelements between the ocean and its sediments, but little is known of the biological, chemical and physical processes which may be responsible for this complex distribution.

10. Pleochroic Haloes and Radioactive Chemistry. G. H. HENDERSON, *Dalhousie University, Halifax, Nova Scotia.*

In the course of an extensive study of pleochroic haloes six distinct types have been recognized. In the two most familiar types the original radioactive elements or parents are uranium I and thorium, respectively. These elements are so long-lived that halo formation could proceed in almost any manner consistent with geological requirements.

Four other types of haloes, tentatively designated as *A*, *B*, *C* and *D*, have rings whose radii indicate that their parents are probably intermediate members of the uranium-radium family. The half-lives of these parents being exceedingly short on a geological time scale, the problem arises as to how a quantity of one of these parents, sufficient to form a halo, could be segregated in the mica. Radioactive evidence thus restricts the possible modes of formation of these haloes and the most probable hypothesis seems to be that they arose from diffusion through the mica of hydrothermal solutions from which the parents were deposited at certain points constituting the halo nuclei. Such an hypothesis appears to satisfy the physical requirements of these types of haloes and if supported by geochemical evidence, throws light on problems of mineralization.

Geology III

Radioactive Methods of Geologic Age Determination

Chairman: DR. A. C. LANE, *Tufts College*

15. Radioactivity and Geochronology. CLARK GOODMAN, *Department of Physics, Massachusetts Institute of Technology, Cambridge, Massachusetts.*

The structural and paleontological methods of correlating geological time are inherently unable to give more than a qualitative indication of age. It is well recognized that a number of important results accrue from the establishment of a quantitative time-scale. The systematic disintegrations of the geologically long-lived radioactive elements provide methods of measuring broad expanses of time, but at present there is some uncertainty in the interpretation of the observations on lead and helium ratios. A direct comparison of these two methods on the same geological materials is complicated by the nature of the disintegration products and the resulting vastly different concentrations in which they occur. Accordingly, no reliable *direct* comparison has yet been made. If there is a clear-cut stratigraphic relationship between the geologic occurrence of a radioactive mineral, suitable for dating by the lead method, and a rock body, suitable for helium age studies, an indirect but sharp comparison may be possible. In general, however, we are dependent upon separate geologic dating of the radioactive minerals and the igneous rocks. Hence, the comparison must be based upon the interdigitation of time scales containing numerous lead and helium ages covering a wide range of geologic time. While the revised helium time-scale is not nearly as complete as the lead scale, sufficient reliable measurements have been made to establish that helium ages, as formerly applied to igneous rocks, are substantially lower than the corresponding lead ages. This disagreement has stimulated a reinvestigation of the fundamental assumptions underlying these radioactive methods. The retentivity of rocks for helium has been found to be extremely variable and is the major source of uncertainty in the application of this method. Metamorphosed rocks are definitely unsuitable for helium age measurements. Recent researches on separate mineral components indicate that, with only a few exceptions, helium ages obtained on rocks as a whole, even fine-grained, unaltered mafic rocks, can only represent minimal values. Certain minerals, notably the feldspars, appear to lose a large fraction of their radiogenic helium. On the other hand, certain of the mafic minerals, pyroxene and magnetite in particular, have a much higher retentivity and show helium ages which approach the values to be

expected from the lead time-scale. Thus, all helium ages made on rocks as a whole represent mean values dependent upon the proportion and helium retentivity of the mineral components. It is anticipated that further research on selected rock minerals will yield helium ages suitable for the establishment of a new helium time-scale in substantial agreement with the present lead time-scale.

16. The Lead Time-Scale. JOHN PUTNAM MARBLE, *Division of Geology and Geography, National Research Council.*

The lead time-scale is based primarily on the value of the ratio $Pb/U+k\cdot Th$, where the correct value of "k" and a proper choice of constants enable us to transform this ratio into years. Since lead exists in nature (apparently) as a stable element, as well as the end-product of radioactive decay, suitable tests must be made to distinguish between radiogenic and common lead in a mineral which carries U and Th. One of these methods, mass-spectroscopy, also gives us an apparently independent check on the "lead ratio," as the "isotope ratio" $Pb^{206} : Pb^{207}$ is also a function of the age of the mineral. Furthermore, a consistent "lead ratio," after correcting for common lead—or, to a lesser degree, without such correction—for minerals of differing Th/U ratio from the same geological formation, affords a valuable second-order check.

It is most important that adequate geologic, mineralogic, and petrographic studies accompany the chemical and physical analyses. The identical sample should be used for all the studies. Unfortunately, lack of material sometimes makes this impossible, and some of the material studied earlier is no longer available.

Where only uranium or thorium (except for very small amounts of the other) are present in a mineral, a determination of the chemical atomic weight of the lead will also indicate the common lead impurity. It is also still worth while to use this value as a check on the isotope ratio.

Among other suggested checks may be mentioned the "oxygen ratio," or ratio of UO_2/UO_3 in a mineral. Theoretically, under certain conditions, this should be of value, but studies so far made do not, in general, lead to a close agreement with the age as otherwise determined.

From the geological side, we can sometimes place an igneous formation which bears radioactive minerals in the relative age-scale. This is truer of formations in post-pre-Cambrian time, but not very frequently the case even here. For the vast extent of the pre-Cambrian we have little confirmatory evidence available, as fossils are absent, and stratigraphic correlations are extremely difficult.

A review of the literature indicates a comparatively small number of determinations which may be given high ranking as possible fixed points in the lead time-scale. These are discussed briefly. Assuming the validity of the present values for the radioactive constants, and hence of the formulae based on them, a tentatively revised lead time-scale is presented.

The complexity of the problem as a whole, and the difficulties involved in the various fields should be emphasized. Analytical methods for the determination of Pb, U and Th, as they exist in minerals, need further study. The proper value to assume for the isotopic composition of common lead, and the various forms of common lead are still under discussion. Further work needs to be done on the relative leaching and weathering of the three elements involved.

17. Helium Retention in Common Rock Minerals. PATRICK M. HURLEY, *Department of Geology, Massachusetts Institute of Technology, Cambridge, Massachusetts.*

In the helium method of age determination the age of the material to be tested is given by the ratio of the content of helium to the content of radioactive elements in the material. The application of the method involves the following basic requirements: (1) A known, systematic rate of disintegration of the radioactive elements; (2) absence of disintegration product as a primary constituent; (3) accurate sampling and measurement; (4) no addition or subtraction of the disintegration product or its source during the history of the material. The first three conditions may be satisfied, it is believed, by careful selection of material, and by cross-checking of measurements by different methods of analysis. A program of work was undertaken, designed to test the fourth requirement.

The radioactive elements commonly occur in the mafic minerals of a rock in larger proportion than in the salic minerals. In an unaltered igneous rock, where, presumably, the minerals are of the same age, it would be expected that the distribution of helium in the various minerals should correspond with the distribution of the radioactive elements, if the fourth basic requirement is satisfied. In each mineral the ratio of helium to radioactivity should be the same. This was found not to be the case. Pyroxene, feldspar and magnetite were separated from six samples of Triassic diabase. Age measurements on each yielded a mean "age" of 103 million years for the pyroxene samples, 104 million years for the magnetite, and 36 million years for the feldspar. The "ages" were closely grouped about the mean value in each case. Measurements on unseparated samples of the diabase gave "ages" between the feldspar and pyroxene in approximately the correct proportion for the mineral composition of the rock. It appears that pyroxene and magnetite retain most, if not all, of their helium, while feldspar loses a part of its helium.

It is concluded that age determinations made directly on rocks containing feldspar are likely to be in error, but that possibly correct helium ages may be obtained by separation and analysis of certain mineral constituents in rocks. Pyroxene and magnetite at present appear to be satisfactory minerals. An age of slightly over 100 million years is indicated for the Palisade diabase of New Jersey.

18. Lead Isotopes and Geologic Time. ALFRED O. NIER, *Department of Physics, University of Minnesota, Minneapolis, Minnesota.*

The computation of the age of a mineral from its lead to uranium or lead to thorium ratio requires a knowledge of the amount of common lead contamination. Ordinarily, this may be readily found from a measurement of the atomic weight of the lead. An isotopic analysis of the lead gives this same information, and, in addition, in the case

of uranium minerals may offer a second method by which the age of the mineral can be checked.

A recent investigation of[1] 12 different samples of common lead indicated that in spite of the nearly constant atomic weight the relative abundances of the isotopes varied from sample to sample. This opens the question as to how to correct for common lead in the radiogenic lead samples. Recently 12 more samples of common lead have been analyzed and variations essentially as large as the previous have been found.

In addition to the above results, isotopic analyses of a number of radiogenic lead samples will be given. The Pb^{207}/Pb^{206} ratio method[2] of measuring geologic age will be fully discussed.

[1] A. O. Nier, J. Am. Chem. Soc. **60**, 1571 (1938).
[2] A. O. Nier, Phys. Rev. **55**, 153 (1939).

Geology IV

Geophysical Applications of Nuclear Physics

Chairman: DR. L. H. ADAMS, *Carnegie Institution of Washington*

31. Radioactivity as a Geophysical Tool. LYNN G. HOWELL, *Humble Oil and Refining Co., Houston, Texas.*

Measurements of radioactivity in geophysical studies have been made both on the surface and in the subsurface of the earth. On the surface, German workers, in several localities, have found high contents of radon in soil gas samples taken over faults. On the Gulf Coast of this country, no correlation between faults and radon content of soil gases has been found. As to gamma-ray intensity measurements made in situ on the surface, little if any change in activity has been observed over faults by the German geophysicists; significant variations over outcropping formations have been found only when the weathered layer is very thin or absent.

In the subsurface, in early work done on samples from wells and tunnels, no great geological significance was attached to the data. However Anbronn found interesting changes in radioactivity in samples extracted in the neighborhood of oil-bearing sands in a well. In Russia, Spak and others made point-to-point measurements of gamma-ray intensities by using a Geiger-Mueller counter inside bore holes.

On the Gulf Coast of this country, we made point-to-point measurements of gamma-ray intensities inside bore holes using an ionization chamber containing nitrogen under high pressure. Pulses proportional in size to the ionization current were produced by periodically grounding the grid of an electrometer tube connected with the insulated electrode of the chamber. At the surface, these pulses were amplified and the throws of an output galvanometer were observed. The curves obtained in the producing section of several oil wells showed correlation with the electrical properties of the formations as found on commercial electrical logs made in these wells.

Following these measurements, a continuously recording apparatus was built using a Geiger-Mueller tube, the amplified pulses from which were fed to a thyratron-controlled frequency meter. The output current of the frequency meter was recorded photographically as a function of depth. In the beginning, two Geiger-Mueller counters were used with separate amplifiers and frequency meters, whereby two independent curves could be recorded simultaneously.

The "gamma-ray logs" disclose a striking correlation with commercial electrical logs made in the same wells, the latter showing the variation of potential of a moving electrode in the well with respect to a fixed electrode and also the variation of formation resistivity or a similar quantity. Through years of use, electrical logs have become a very important tool in correlating geological formations. An obvious advantage of the gamma-ray over the electrical method, is that logs can be made inside wells cased with iron pipe, which offers too much shielding action for electrical measurements but does not seriously absorb the penetrating gamma-rays.

In general, sands are low in radioactivity in comparison with shales. So far, no marked characteristics have been found which distinguish oil-bearing from water-bearing sands.

A different application of this technique of measuring radioactivity in wells has been found in the location of cement which has been pumped behind the casing in a well. Carnotite, a radioactive ore, was added to the cement before it was pumped out through perforations or through the lower end of the pipe. The presence of the carnotite was detected by measuring the variations of gamma-ray intensity with depth inside the casing.

32. The Internal Heat of the Earth. L. B. SLICHTER, *Department of Geology, Massachusetts Institute of Technology, Cambridge, Massachusetts.*

The most important factors in the problem of the earth's internal heat are taken to be the following six: (1) The gain of heat from radioactive sources throughout the interior; (2) The loss of heat as measured by the upward heat flux in the earth's crust; (3) The original heat of the earth, as represented by the initial temperautre distribution when the crust first solidified; (4) The value of the thermal conductivity, and its change with depth; (5) The presence or absence of significant heat transport by convection currents in the interior; (6) The large heat capacity and thermal inertia of the earth.

1. The recent measurements by Evans and his coworkers are adopted as affording the most reliable values for the heat generated in rocks. If these results be used to

compute the heat generated in an earth-model such as proposed by Washington, it results that the total heat being generated is about tenfold greater than that being lost. This result is typical of others, deduced from other proposed earth models. Several reasons are presented for believing that the estimates of the heat-gain based upon these models may far exceed that actually occurring in the earth.

2. Measurements by Ingersoll, Bullard, Benfield and others indicate that the mean value of the heat loss in continental areas is not far from 1.2×10^{-6} cal./cm²/sec.

3. Fundamental difficulties preclude satisfactory estimates of the original temperatures in the earth. No satisfactory data are available from which to estimate the change of melting point of rocks with pressure. Hence the original temperature gradients in the solidified earth are unknown.

4. It is possible that the thermal conductivity at depth differs significantly from its surface values. It is well to admit a generous range of possible values for the thermal conductivity at depth.

5. If they exist, thermal convection currents having a velocity as small as one kilometer per million years, would transport about a hundred fold more heat than would the thermal conductivity. It is conceivable that convection may exist and may maintain an essentially adiabatic temperature distribution at depth.

6. The enormous heat capacity of the earth is significant. Indeed, the observed rate of heat loss could be maintained throughout the earth's lifetime with only a small percentage decrease in internal temperatures, and without any contribution from radioactivity. Because of the size and heat capacity of the earth, temperature decreases at depth must occur exceedingly slowly. Without radioactivity, a decrease of the order of 1°C in 10 to 50 million years may be expected. With radioactivity, a net increase of at least 30° per million years is indicated, provided the minimum values of radioactivity observed in available surface samples are realized at depth. It is shown that heat sources of considerable magnitude may exist at depth without being detected by thermal observations at the surface. It is uncertain whether the earth is heating, or cooling at depth. Geological evidence supports no distinct trend either in one direction or the other. It is of interest, then, to examine the middle possibility; namely, the equilibrium temperature state. Steady-state temperature distributions are computed for a number of different distributions of the radioactivity and of the conductivity.

In summary, it is obvious that thermal evidence alone does not suffice to yield definite results about thermal conditions in the interior. However, evidence from independent sources is sometimes available and helpful. For example, the large increase in electrical conductivity at depths below 500 km deduced from studies in terrestrial magnetism has significance. More accurate knowledge of the variation of seismic wave velocities in the mantle may prove helpful. The fluidity of the earth's core, as deduced from several types of geophysical evidence, obviously has important thermal implications. Finally, future contributions from atomic theory concerning the probable mechanical and thermal constants of rock-materials in the deep interior would distinctly advance our deficient understanding of the problem of the earth's internal heat.

33. Earth Heat and Geological Processes. DAVID GRIGGS, *Harvard University, Cambridge, Massachusetts.*

The internal heat of the earth is the only known reservoir of energy which is sufficiently large to have served as a source for the primary processes of geology which formed the surface features of the earth exemplified by our mountain chains. In choosing between the various physical hypotheses of the mountain-building mechanism, the two most important considerations are: (1) the distribution of temperature within the earth, and (2) the proportion of the surface heat loss which is due to the primary heat of the earth compared to that due to radioactive heat. The answer to both these questions depends on knowledge of the distribution of radioactivity within the earth. It is the purpose of this paper to reexamine the hypotheses of mountain-building in the light of recent measurements of physical constants and estimates of the radioactivity in the earth.

Metallurgy I

Tracer Studies of Metal Diffusion

Chairman: DR. F. SEITZ, *University of Pennsylvania*

5. The Importance of Diffusion in Physical Metallurgy. R. F. MEHL, *Metals Research Laboratory, Carnegie Institute of Technology, Pittsburgh, Pennsylvania.*

It is the purpose of this paper to present a discussion—in an informative and descriptive rather than an analytical manner—of the metallurgical phenomena in which diffusion plays an important or a dominant role. This abstract will merely list these phenomena.

The freezing of alloys; segregation; solid solution and heterogeneous segregation; annealing of ingots and forgings, homogenization, and diffusion; directional properties in forgings; banding.

Treatment of alloys of the age-hardening type; the process of age-hardening; ingot segregation; ingot breakdown and homogenization anneal; solution heat-treatment; quenching and precipitation hardening; concentration

fluctuations and diffusion in the solid solution; theory of nucleation; particle growth; time-temperature relations in aging; interaction and activation energies.

Steel-treating and quench hardening; constitution of annealed steel at room temperature and at high temperatures; constitution of steel on slow cooling, on quenching; α Fe, Fe_3C, γ Fe, pearlite, austenite, martensite; rate of solution of carbides on high temperature annealing; formation of pearlite, nucleation and growth, effect of austenite grain size and of alloy content; interlamellar spacing, rate of formation of pearlite; rate of diffusion of carbon in austenite; martensite and hardening; decomposition products of austenite, diffusion and nondiffusion reactions; tempering of martensite and spheroidization of pearlite.

Diffusion in solid-gas systems; carburizing of steels, depth of carburizing, rates and variables; dezincing of brass on annealing, calculation from rates of diffusion, effect of grain size; nitriding and diffusion of nitrogen in α iron; oxidation of metals and alloys, constitutional relationships, nature of oxide films and scales, rates of oxidation, mechanism of diffusion through oxide films and scales, variation of rates with crystal orientation, temperature, time, and gas pressure, effect of alloy content, scaling-resistant alloys and mechanism of oxidation internal oxidation, embrittlement of copper.

Metallic diffusion coatings; chromizing, siliconizing, sherardizing; structure and properties. Veneer metals and bimetallic strip; diffusion bonding. Powder metallurgy; preparation of alloys by annealing of mixed metal powders; diffusion. Annealing of multiple electrodeposits; types and thickness of phase layers and rate of formation of layers.

Self-diffusion; processes in single metal phases analogous to self-diffusion; recrystallization, nucleation and growth of recrystallized grains, rates and activation energies; creep and activation energies; crystal plasticity and forming operations.

6. Atomic Mechanisms of Diffusion. R. P. JOHNSON, *Research Laboratory, General Electric Company, Schenectady, New York.*

The conventional diffusion coefficient $D(T,c)$ for a binary alloy is a measure of the rate of disappearance of an infinitesimal chemical nonhomogeneity in the alloy. Its value depends on the detailed mechanism of atomic place-changes, but so many other factors enter that it is practically impossible to use the measured diffusion coefficient for deciding among various possible models of the motion of atoms past one another.

On the other hand, if one marks (by means of radioactivity) some of the atoms of one element of the alloy and studies the diffusion of these marked atoms, keeping the chemical composition of the entire specimen at all times homogeneous, one can calculate directly from the measured diffusion coefficient the average number of elementary moves made by an atom of that element during the time of the experiment. This is a quantity that can be predicted theoretically, once a model for the place-change mechanism has been adopted. A comparison between the observed number of moves and the predicted number will test directly whether the imagined mechanism is satisfactory. The temperature and the composition of the homogeneous binary alloy can be varied, and at each temperature and composition two quantities, the average number of moves made in unit time by each of the two components, can be measured and compared with predicted values. In principle it is possible by the same method to measure the motility of any element in any homogeneous surroundings however complicated.

This use of tracer-atom techniques yields direct information about the mechanism of atomic migration, which can be had by no other means. It is not to be confused with the use of radioactive atoms in diffusion experiments of the conventional type, where they serve merely as convenient indicators of the concentration of inert nuclei of the same chemical kind.

7. Radioactive Methods in Diffusion. P. H. MILLER, JR., *Randal Morgan Laboratory of Physics, University of Pennsylvania, Philadelphia, Pennsylvania.*

In the measurement of diffusion in solids using radioactive indicators (either artificial or natural), a sample is used which has a non-uniform distribution of some radioactive isotope and the change of distribution is determined as a function of time. For mathematical convenience it is convenient to have an infinitesimal and plane layer of radioactive material placed upon an inactive sample as the initial distribution. This has been accomplished by electroplating, evaporation and the collection of radioactive disintegration products from a gas. These procedures have the disadvantage that the exact conditions at the surface of contact are unknown. Secondly, samples have been prepared by rolling together an inactive metal foil with an active one of finite thickness. Finally, radioactive isotopes have been formed in the sample itself by bombarding it with neutrons; other nuclear particles could be used. This method of activation has the advantage of being simple and avoids any possibility of the existence of a boundary disturbance between the active layer and the bulk of the sample.

There are various methods of measuring the change in distribution which is a result of the diffusion process. If Dt, where D is the diffusion coefficient and t the time for which the sample is kept at high temperature during which the appreciable diffusion takes place, is greater than 10^{-5} cm^2 the sample can be cut into sections (say 4×10^{-3} cm thick), mechanically and the activity of each section measured. This is the most direct method for the surface effects can be eliminated and Fick's law $\partial c/\partial t = D\partial^2 c/\partial x^2$ which is assumed in all the other methods can be checked. It has the disadvantage that each sample can be used only once. The activity is measured with a counter or electroscope and in the case of α-particles by counting scintilations on a zinc sulphide screen. Since the particle radiation is strongly absorbed the activity of a sample will fall off as the radioactive atoms diffuse into the interior, and the activity of the inactive side of the sample which is usually made slightly thicker than the range of the emitted particles will

increase. This method has been used for values of Dt greater than 10^{-10} cm². Here the absorption coefficient and the half-life of the radioactive isotope must be accurately known. Since the range of the recoil atoms is extremely short they provide an even more sensitive method and can be used for values of Dt greater than 10^{-12} cm². The recoil atoms are collected on a charged plate and in cases where they are radioactive their number determined from this property.

The diffusion of lead in ionic crystals under the influence of an electric field has been investigated for certain lead salts and has given valuable information as to which ions are transferring the charge. The use of artificially radioactive atoms will extend this method and give much useful information.

Measurements of diffusion in liquids have been made using radioactive indicators but there is no practical advantage in this method except in the case of self-diffusion.

Metallurgy II

Metallurgical Applications of Nuclear Physics

Chairman: DR. C. S. BARRETT, *Carnegie Institute of Technology*

11. Radiography with Gamma-Rays. JOHN T. NORTON, *Department of Metallurgy, Massachusetts Institute of Technology, Cambridge, Massachusetts.*

Gamma-rays from radioactive sources are used in industry for the inspection of heavy castings and weldments. The radiograph is in effect a shadow picture of the object, recorded photographically, and defects which represent a change in thickness of the object are shown as shadows on the film. The technique is simple and straightforward.

Since radiographic inspection depends upon the absorption of the radiation in the object, the wave-length distribution and conditions of scattering of the radiation are of primary importance. The very short wave-length of gamma-radiation results in a low absorption in the object so that large thicknesses of metal can be examined. At the same time, the low absorption permits the examination of a considerable range of thicknesses at a single exposure. For many classes of work this is of the greatest practical importance. On the other hand, the low absorption reduces the ability to detect the smallest defects in the object and this is a very real disadvantage. The scattering of the radiation within the object is not particularly troublesome in the case of gamma-radiation.

It is of interest to compare the practical application of gamma-ray inspection with that carried out by means of x-rays. In the case of x-rays generated at 200 to 300 kv, the two methods really fall into separate classes. The x-ray method is capable of greater sensitivity in detecting small defects and requires short exposures. The gamma-ray method will handle much greater thicknesses of metal, has a greater latitude in recording differences in thickness of the object, and has the advantage of excellent portability of the radiation source. If the x-rays are generated at 1000 to 1250 kv, the physical characteristics of the radiation are similar to gamma-radiation but the very much greater intensity makes the exposure a matter of seconds rather than hours. In this case, one would have to balance the greater complexity of the radiation source against the material saving of exposure time.

The industrial use of radiographic inspection always involves some sort of compromise to obtain optimum working conditions. This compromise can be made to the best advantage if the fundamental factors underlying the problem are understood.

12. Tracer Studies in Metallurgy. WILLIAM A. JOHNSON, *Westinghouse Research Laboratories, East Pittsburgh, Pennsylvania.*

Radioactive materials have not enjoyed an extensive application in metallurgical studies, but a number of experiments have been reported which indicate an increased use of them in the future. Such experiments may be divided roughly into three groups: the measurement of rates of self-diffusion; the determination of changes in surface and internal structure by the Hahn emanation method; and the detection of segregation and cracks by contact photographs.

The first measurements of the rate of self-diffusion were made by von Hevesy in 1920, using ThB as an indicator in lead. Recently, other metals have been studied, using artificially radioactive isotopes: gold by Sagrubskij and McKay; copper by Rollin and Steigman, Shockley and Nix; zinc by Miller and Day, and Banks and Day; and silver by Johnson. Several experimental procedures have been employed. The active isotope may be electrolytically plated on the nonactive isotope; a thin foil of active material may be rolled onto the nonactive base; and an active layer may be produced on a stable base by direct bombardment by particles of low penetrating power. Two general methods have been used for determining the diffusion coefficient after heat treatment. The earlier method, and the one of more use when short-lived isotopes are employed makes use of the absorption of ionizing particles by the metal into which the active atoms diffuse; the diffusion coefficient may then be calculated from a knowledge of the decrease in activity of the active surface after diffusion, and the absorption coefficient of the metal for the particles emitted (usually β-rays). This method suffers from the disadvantages that there is no check on the quality of the interface between active and inactive layers, and that quite small errors in measuring the activity may produce large errors in the diffusion coefficient. In the

second method, the diffusion specimen is cut into thin layers parallel to the original interface, and the activity of each layer is determined. The diffusion coefficient is then easily calculated from standard equations. Self-diffusion measurements have not been very satisfactory in the past, but more careful attention to detail, and the use of the sectioning method should yield better results in the future.

The Hahn emanation method has been applied to metallurgical problems by Werner, Seith, and others. An active material (usually thorium X) is introduced in very small amounts into the metal under investigation by melting, electrolysis, or diffusion. The noble gas thoron produced in the disintegration of thorium X diffuses out of the specimen and may be measured. It is found that the activity of such specimens increases smoothly with temperature; if structural changes occur in the metal—recrystallization, polymorphic transformation, welding of pressed powders—there is a sudden change in the emanation from the specimen. Such changes may be detected with good accuracy by this method, but its advantages over other methods have not yet been clearly demonstrated.

Tammann has used thorium B to reveal segregation and ingot structure in cast metals. A small amount of active material (10^{-6} weight percent) is incorporated in a specimen by melting and, after polishing, a photographic plate is placed on the smooth surface. An exposure time of 24 hours is sufficient, and after development, dark areas on the plate reveal the position of the active material in the specimen. This procedure clearly reveals the segregation and dendritic structure of castings and should become a valuable tool in the future.

Kaiser has recently described a very similar method for locating fine cracks in polished surfaces. The active material is carried in a grease which is forced into the invisible cracks by high pressure. After removing all excess active grease, a plate is exposed, which, upon development, shows the position of cracks. This procedure has not been sufficiently refined to compete with the Magnaflux method for ferrous materials, but may prove important for nonferrous materials.

13. Outlook for Use of Neutron Scattering in Studying Ferromagnetic Substances. F. BLOCH, *Department of Physics, Stanford University, Stanford University, California.*

The fact that neutrons, although carrying no charge, have a magnetic moment has been experimentally verified and the neutron moment has been measured. Being about a thousand times smaller than ordinary atomic moments it is, nevertheless, big enough to contribute essentially to the scattering of slow neutrons in magnetized bodies. This is due to the interaction of the neutron moment with the amperian molecular currents which cause magnetism. Any quantitative prediction of this so-called "magnetic scattering" of neutrons has to make rather detailed assumptions as to the size and distribution of the amperian currents. It is feasible, on the other hand, to use it as a tool to obtain more detailed knowledge about those characteristic features of magnetism, particularly of ferromagnetism, which do not show up in the magnetization curve. At the present moment two rather separate groups of problems seem tangible and of interest.

The first group centers around investigations of the amperian currents themselves. As in the determination of "atomic form factors" by means of the scattering of x-rays the dependence of the magnetic scattering on the energy and the angle of scattering of slow neutrons must yield a characteristic "magnetic form factor." The determination of this quantity would make it possibleto trace the amperian currents within the elementary magnets and should clearly exhibit the role that valency electrons may play in ferromagnetism. This seems to be particularly interesting with respect to those ferromagnetic alloys which consist of nonferromagnetic elements.

The second group is suggested by the discovery that the magnetic scattering shows a sharp increase and subsequent saturation within the last few percent of the magnetic saturation. It is most likely that this phenomenon is due to rather macroscopic features of ferromagnetic substances. Since the magnetization curve exhibits the result of the "turning in" of the various Barkhausen regions the approach of saturation must mean that practically all these regions have found their proper orientation. One can understand, however, that a very slight deviation from saturation will still offer enough space within the substance practically to destroy the polarization effect of the magnetic scattering by rapid precession of the neutron moment around the direction of the magnetic inductance. Thus this last lack of saturation, hardly noticeable in the magnetization, seems to be very pronounced in the magnetic scattering of neutrons. If so, single crystals should, in this respect, behave very differently from polycrystalline materials; the further investigation of this effect will furnish more information about the relation between grain-size, mechanical treatment, etc., and the saturation of ferromagnetic substances.

14. Neutron Studies of Order in Fe-Ni Alloys. F. C. NIX, *Bell Telephone Laboratories, New York, New York;* AND H. G. BEYER AND J. R. DUNNING, *Columbia University, New York, New York.*

Neutron transmission measurements are used to study order in Fe-Ni alloys. The difference in neutron transmission between fully annealed and quenched alloys when plotted against the nickel content displays a broad peak around Ni_3Fe and falls to vanishingly small values near 35 atomic percent Ni and pure Ni. The higher the degree of order the greater the neutron transmission. The substitution of 2.3 atomic percent Mo or 4.1 atomic percent Cr for Fe in the annealed 78 atomic percent Fe-Ni alloy caused a decrease in the neutron transmission, relative to the annealed 78 atomic percent Fe-Ni alloy, of 15.6 and 21.2 percent, respectively. The cold working of an annealed binary 75 atomic percent Ni alloy, a treatment known to produce disorder, gave rise to a decrease of 20.6 percent in neutron transmission. These results demonstrate that neutron techniques serve as a useful tool to study order in Fe-Ni alloys, and suggest that they can be extended to study other solid state phenomena.

Chemistry I

Tracer Techniques in General Chemistry

Chairman: DR. H. S. TAYLOR, *Princeton University*

19. Radioactive Methods in the Study of Co-precipitation and Adsorption. KASIMIR FAJANS, *Department of Chemistry, University of Michigan, Ann Arbor, Michigan.*

The paper consists of two parts. In the first part, a brief review is given of the development of the subject since the early days of radioactivity. In the second part, are described experiments, as yet unpublished, which, by use of artificially produced radioactive isotopes, help to clarify the mechanism of the adsorption of dyestuffs.

The precipitation rule (Fajans and Beer, 1913) and the adsorption rule (Paneth and Horovitz, 1914) emphasize the insolubility as an important factor for the elimination from the solution of an element present in extremely small concentrations.

Investigations with von Beckerath (1921) and Erdey-Grúz (1931) and those of Hahn (1926) have demonstrated that the adsorption of a radio-element increases when the adsorbent has a charge opposite in sign to that of the element and is decreased, but not always excluded, by a charge of like sign.

These results when applied with Hassel (1923) to the adsorption of organic dyestuff anions and cations on silver halides led to a new type of indicators for volumetric analysis, named by Kolthoff adsorption indicators.

The dyestuffs can be measured in small concentrations because of their intense color, which imparts to them properties of indicators or tracers, as radioactivity does in the case of elements. The combination of both types of indicators has been applied, e.g., for the determination of the area of the adsorbent surface (Paneth), investigations of the aging of precipitates (Kolthoff), indirect estimation of relative adsorbability of ions (with Erdey-Grúz).

Two main mechanisms of adsorption of ions were discussed:

1. The attachment of the adsorbed ion to the oppositely charged ion of the lattice surface: addition mechanism.

2. The replacement by the adsorbed ion of a lattice ion of the same sign: exchange mechanism (applied by Kolthoff especially in case of dyes).

The two mechanisms lead to different expectations in the case of adsorption of dye anions in the presence of an excess of lattice cations. Experiments with Gretchen Mueller (1939) have shown that the saturation values for the adsorption, e.g., of eosin on silver bromide increase considerably with the silver ion concentration. This supports the addition mechanism and cannot be reconciled with Kolthoff's theory. Further experiments were performed with Amos Newton, using radioactive indicators.

Eosin and erythrosin were adsorbed on silver bromide precipitates containing radioactive bromide. In case of eosin an excess of silver ions was used. No increase of the activity of the solution was found, showing that no noticeable exchange of the dye anion with the bromide ions of the lattice surface takes place. Thus the adsorption must be due predominantly or wholly to the deposition of eosin ions on the silver ions of the adsorbent.

In the case of erythrosin, which is adsorbed considerably even in the presence of an excess of halogen ions, no excess of either ion was used. It was found that for each adsorbed erythrosin ion about two bromide ions are brought from the adsorbent to the solution. This result is not a proof for a direct exchange between the adsorbed erythrosin ion and the bromide ion of the lattice.

In fact, the solubility of silver erythrosinate is 1×10^{-6} m, that of silver eosinate 5×10^{-5} m. The considerable adsorption of eosin on silver bromide from a solution containing only 1×10^{-5} m eosin and silver ions can be formally considered as a two-dimensional precipitation of silver eosinate below its normal solubility product. Thus in the presence of the adsorbent the solubility product of silver eosinate is diminished.

This means, when applied to silver erythrosinate, that its "solubility" in the presence of silver bromide is diminished below 1×10^{-6} m and thus becomes of the same order of magnitude as that of silver bromide itself (5×10^{-7} m). In such a case the precipitation of erythrosin from the solution containing no excess of silver ions must be accompanied by dissolution of silver bromide and it is this secondary phenomenon which causes the radioactive bromide ions of the adsorbent to appear in the solution.

For different reasons, e.g., because of the results of light absorption measurements with Marie Farnsworth (1937), the addition mechanism appears to be the most probable also for the primary adsorption of erythrosin ions.

By using radioactive sodium it was found that the adsorption of eosin and erythrosin on silver bromide is not accompanied by an adsorption of the sodium ions. This agrees with similar results of Kolthoff (1935) obtained in other cases.

20. Measurement of Vapor Pressures and Solubilities of Certain Thorium Compounds by Radiochemical Methods. RALPH C. YOUNG, *Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts.*

Radiochemical methods are being devised on an ever increasing scale for the study of many hitherto unsolved problems in inorganic and physical chemistry. Reference is here made to the measurement of vapor pressure and of solubility.

Thorium acetylacetonate can be sublimed readily at 160° at a pressure of 1 mm. It is similar in many respects to the acetylacetonates of the rare earth metals. These, however, decompose below a temperature at which any marked rate of sublimation occurs and consequently this property has not been used for their separation. At 100° the rare

earth acetylacetonates are, in general, stable and their vapor pressures would likely be of the same order of magnitude as that of the thorium compound. Because it is so low, this value could not be obtained by the usual procedures, but a radiochemical method was found adaptable.

A known volume of inactive nitrogen was saturated with thorium acetylacetonate by being passed through a long column of the compound maintained at 100°, and was subsequently directed into hydrochloric acid where the vapor of the acetylacetonate was converted into thorium chloride. The vapor pressure was calculated by use of the perfect gas equation, $PV=nRT$, and the molal quantity of the thorium compound in the gas mixture obtained by means of its radioactivity. A comparison of the alpha-count of a deposit from an aliquot part of the chloride solution with that from a standard solution of thorium chloride prepared from a known weight of the acetylacetonate provided data for the necessary calculation. The alpha-counter used was of the parallel plate condenser type with photographic recording device described by Finney and Evans. A rapid stream of nitrogen was passed through the ionization chamber in order to prevent the accumulation of thoron. From measurements of the deposits of the standard solution it was found that 1×10^{-6} g of thorium acetylacetonate gave an alpha count of 7.3 ± 0.7 per hour 10 months after the preparation of the compound from thorium nitrate. The value at equilibrium was calculated as 9.0 ± 0.9. The theoretical count based on $\frac{1}{2}$ of the total activity of four alpha-emitters is 10.9. By means of the foregoing standardization and the alpha-counts of deposits from solutions derived from the sublimed acetylacetonate, which gave 50 to 100 alphas per hour above a background of 20, the vapor pressure of the thorium compound at 100° was calculated as $3.2\pm0.3\times10^{-4}$ mm.

Thorium pyrophosphate, a salt of two tetravalent ions, has long been used in the analytical chemistry of thorium. The effect of salts on the solubility of a salt of this type is of great interest to those engaged in the study of solution theories. Because of the great insolubility of thorium pyrophosphate a radiochemical method has been used for this study. Salt solutions were allowed to pass at rates which insured saturation through a thermostated cell containing a long column of the thorium compound. Deposits were made from these solutions on small copper dishes which were subsequently covered with a cellulose acetate glyptal film, the purpose of which was to retain the thoron but allow passage of the alpha-particles. To convert the alpha-counts of such deposits into grams of thorium pyrophosphate, it was necessary to obtain an alpha-absorption coefficient for each salt. This was accomplished by comparison with the alpha-activity of deposits of a standard thorium chloride solution with and without added salts. The solubility of thorium pyrophosphate was found to be 6.1×10^{-5} g per liter at 25°. The added salts have a very marked effect on the solubility. For example, in a solution of copper chloride containing 13.5 g per liter, the pyrophosphate was over 100 times as soluble as in pure water, and about 170 times as soluble in a solution of copper sulphate containing 16 g per liter. These results are in accord with the theory of Debye.

21. Use of Stable Oxygen Isotopes in Tracing Reaction Kinetics. IRVING ROBERTS, *Weiss and Downs, Inc., New York, New York.*

The production at Columbia University of sizable amounts of water containing an increased concentration of the oxygen isotope of mass 18 made possible the discovery of a new series of reactions, namely, oxygen exchanges between organic compounds and water. The kinetics of such reactions are interesting because they proceed at measurable rates with no change in medium, and because they exhibit acid and basic catalysis. In addition, their mechanisms are related to those of well-known organic reactions, and may shed some light on the latter.

For example, in the exchange of oxygen between benzoic acid and water, the reaction in dilute solution is found to be first order in the difference of O^{18} content of the reactants and independent of the concentration of benzoic acid. An equation expressing these kinetics may be derived from a consideration of the nature of the reactions and the statistical factors involved in the system. In addition, it is observed that the rate of the reaction is proportional to the hydrogen ion concentration in the reaction mixture.

A comparison of this reaction with those of acid catalyzed ester hydrolysis and esterification shows the following similarities: (1) The reactants and products are structurally similar. (2) All three reactions are catalyzed by acids. Esterification and ester hydrolysis are known to exhibit general acid catalysis. (3) The rates of all three reactions are of the same order of magnitude. (4) Heavy oxygen studies have shown that in all three reactions, the same linkage is broken, namely, the carbon-oxygen bond of the acid or its residue.

On the basis of the above, it is concluded that the three reactions are similar in mechanism, and that these mechanisms will be symmetrical ones, i.e., that the reverse of the mechanism for esterification will be a mechanism for hydrolysis which is similar to it. The mechanism of the exchange reaction will of course be symmetrical.

From the existence of the equilibrium relationship

$$\frac{\text{moles ester}\times\text{moles water}}{\text{moles alcohol}\times\text{moles acid}}=K$$

it is argued that the esterification and hydrolysis are first order in alcohol and water, respectively. While equilibrium data do not generally prove kinetic dependences, a comparison of this particular system with the exchange reaction indicates this conclusion to be very probable. In addition, there are some kinetic data which show a first-order dependence of esterification rate on the alcohol concentration.

Granting that the exchange, esterification and hydrolysis reactions are general acid catalyzed and first order in alcohol or water, there are three possible mechanisms which fit these requirements. Two of these consist of a series of bimolecular steps, and the third is termolecular in nature. At the present time, there seems to be no method of distinguishing among these possibilities.

However, it is evident that the combination of the results of heavy oxygen studies with previous kinetic data has

resulted in the elimination of the many possible mechanisms which may be proposed, down to three which are most probable.

22. The Thermal Exchange Reactions of Mg, Cu, Mn, Fe, Cl, Br, I and Hg Studied by Their Radioactive Isotopes. S. RUBEN, G. T. SEABORG AND J. W. KENNEDY, *Department of Chemistry, University of California, Berkeley, California.*

Radioactive Fe^{59} (47 days half-life) was used to study some exchange reactions of iron. An immeasurably rapid exchange of electrons between ferrous and ferric ions in 6*N* hydrochloric acid at room temperature was found. No electronic exchange between aqueous ferrocyanide and ferricyanide ions was observed even after four days at room temperature. No exchange of iron atoms was observed between any of the following pairs of substances: ferric and ferricyanide ions, ferric and ferrocyanide ions, ferrous and ferricyanide ions.

Two other instantaneous exchanges, which may also proceed by an electron transfer mechanism, were observed to occur in aqueous solution at room temperature. The 43-min. Hg^{197} was used to show that mercurous and mercuric ions undergo rapid exchange and experiments with the 2.6-hr. Mn^{56} have revealed a rapid exchange between manganate and permanganate ions in alkaline solution.

Radioactive Cl^{38} (37-min.), Br^{82} (34-hr.) and I^{131} (8-days) have been used to study the measureable rates of exchange between these halogens and their corresponding halogenates in acid solution at room temperature.

The 10.2-min. Mg^{27}, 47-day Fe^{59} and 12.8-hr. Cu^{64} have been used to measure the exchanges at room temperature between the corresponding metallic ions and some metal-organic compounds. There was no exchange in 40 min. between magnesium ions and highly purified samples of either chlorophyll *a* or chlorophyll *b* in a buffered 80 percent acetone solution. The exchange between magnesium ions and the magnesium compound of 8-hydroxyquinoline proceeds rapidly in aqueous ethyl alcohol solution. There is no exchange between ferric ions and ferrihemoglobin in aqueous solution or between ferric ions and ferriheme in ethyl alcohol even in experiments lasting several weeks. The exchange between copper ions and copper acetylacetonate in chloroform is complete within 2 min. Some of these results are rather surprising in view of other evidence concerning the bonds in these metal-organic compounds, and hence give additional valuable information about these bonds.

Chemistry II

Tracer Techniques in Analytical Chemistry

Chairman: DR. H. C. UREY, *Columbia University*

34. Use of Isotope Tracers in the Study of the Composition of Proteins. DAVID RITTENBERG, *College of Physicians and Surgeons, Columbia University, New York, New York.*

The analytical chemist is able to analyze a mixture only when he has available a specific reagent for the substance to be determined. This reagent must give a reaction, either a precipitate, color, or other indication, with only one constituent of the mixture.

Proteins when hydrolyzed give rise to a mixture of from 15 to 20 alpha-amino acids. For some of these there are known specific reagents which precipitate them. For others there are known reagents which give color reactions which can be made quantitative. For the majority no such reagents are known.

To make a quantitative determination of the amount of such an amino acid present in a mixture one must isolate all of the amino acid in a pure state by some suitable fractionation procedure. The two conditions are, in practice, mutually contradictory. One can isolate all of an amino acid in an impure state, or some of the amino acid in a pure state.

The isotope dilution procedure requires the isolation of only a pure sample of the substance to be determined, the yield being unimportant.

If, to a mixture of amino acids, is added x grams of glycine containing C_0 atom percent excess of N^{15} (or C^{13}), this glycine will mix with the glycine already present and form an inseparable mixture. If, now, glycine is isolated and found to contain C atom percent excess of N^{15}, then the original amount (y) of glycine in the amino acid mixture is given by Eq. (1),

$$y=[(C_0/C)-1]x. \tag{1}$$

As, by this method, only a small sample need be isolated, merely enough for an isotope analysis (about 5–15 mg), large losses may be permitted during the purification process. By the proper choice of experimental conditions the error of the method may be reduced to about one percent.

All the amino acids with the exception of glycine exist in two enantiomorphic forms. In protein, the *l*-configuration is found almost exclusively. By the addition of a *d-l* mixture and isolation of both the *l* and *d* components or of the *l* and *dl* components, the amino acid content of both the *l* and *d* can be calculated. By this method the extent of racemization of glutamic acid of normal and tumor tissue has been found to be very small.

The same method can be employed in the estimation of fatty acids in fats.

This method can be so modified that even though the amino acid isolated is quite impure (contains 10 percent impurity), the analytical result will not be in error by more than one percent.

35. Applications of Radio-elements in Analytical Chemistry. CHARLES ROSENBLUM, *Frick Chemical Laboratory, Princeton University, Princeton, New Jersey.*

The sensitivity with which radio-elements may be detected and quantitatively measured makes them admirably suited for use as isotope indicators in analytical chemistry. In general such indicator experiments fall into two groups, one which depends upon the chemical inseparability of isotopes once mixed, and a second in which a change in ratio of active to stable isotope occurs. When the isotopic ratio remains constant, the indicator is a true "tracer" element; and its radiations reveal the presence and concentration of the inactive form throughout a given system. Most analytical applications belong to this group. Those applications in which the isotope ratio varies are of equal interest in that frequently they cast light upon the mechanism of processes of fundamental importance to the analytical chemist.

The relatively limited reproducibility of electroscope and counter measurements when compared with that of the usual quantitative analysis restricts the use of radio-elements to the field of microchemistry. However, here their usefulness is amply illustrated by solubility determinations on certain lead-, cobalt- and phosphorus-containing compounds, as well as by studies of adsorption and coprecipitation phenomena at low concentrations. Even in ordinary analytical chemistry, when a gravimetric separation is uncertain or undeveloped, the activity of a component containing a radioactive isotope furnishes a simple and rapid means of locating it, and permits one to work out proper precipitation conditions. Going a step farther, it is evidently possible to determine just how far an analysis is in error and to make the proper correction. Furthermore, a whole system of radiometric microanalyses, based on precipitation reactions with thorium B, has been proposed by Ehrenberg.

Generally speaking, the radio-elements are so sensitive to detection that it is possible to test the limit of validity of any analytical procedure, be it the efficacy of washing a precipitate, the completeness of a precipitation reaction, or the lower limits of applicability of fundamental laws. Thus the distribution of a solute between phases, so important in crystallization and extraction processes, has been studied, in addition to the law of mass action and the Nernst electromotive force law. Indeed, the latter has been shown to hold for bismuth in concentrations as low as 10^{-12} normal, and has been suggested as the basis for determining minute quantities of this element.

Aside from being useful in routine analytical procedures, radio-elements have proven to be of service in examining the mechanism of certain fundamental reactions as well as in studying the nature of a number of common analytical precipitates. They have disclosed unsuspected changes which take place during the aging of precipitates such as lead sulfate and silver bromide. Such observations have led to a better understanding of the perfection processes which occur during this period of change and which are often characterized by a liberation of contaminating impurities. Not only have the external surfaces of such solids been measured by means of radio-elements, but the easy accessibility of ions at the interior of fresh precipitates has been demonstrated. Judging from the above examples it is evident that analytical chemistry offers a fertile field for further indicator researches.

36. The Contribution of Artificial Radioactivity to the Completion of the Periodic System. EMILIO SEGRÈ, *Radiation Laboratory, University of California, Berkeley, California.*

At the time of the discovery of artificial radioactivity, four elements with atomic number lower than 92 were still unknown, *viz.*, elements 43 (eka-manganese), 61, a rare earth, 85 (eka-iodine) and 87 (eka-caesium). Element 87 has been found by Mlle. Perey[1] as a rare branching product in the natural radioactive actinium family. Perrier and Segrè[2] found element 43 among the products of neutron and deuteron bombardment of molybdenum; element 61 has probably been produced by the bombardment of neodymium with deuterons,[3] but, because of the well-known difficulties connected with the separationof the rare earths, no chemical studies have been undertaken on 61. Corson, MacKenzie and Segrè[4] have prepared element 85 by the bombardment of bismuth with alpha-particles.

The essential contribution of artificial radioactivity to the discovery of new elements is that these substances, with the exception of element 87, can be artificially prepared by transmutation and can be easily detected through their radioactivity. The amounts of these elements which can be artificially produced is extremely minute (10^{-10} to 10^{-14} gram), but using the methods of radioactive chemistry it is possible to attain a fairly complete knowledge of their properties.

This information makes it possible to predict geochemically the probable ores in which these elements could be found, should they exist in nature, and to devise suitable methods for their concentration. Moreover, the use of the artificially prepared element as a tracer would make it possible to check directly each step of the extraction. These points are of considerable importance since it has been found in certain instances that the chemical properties suggested by the analogies of the periodic system are significantly different from some of the observed properties of these new elements. These differences between the predicted and observed chemical properties of element 85 are sufficient to invalidate the past attempts to isolate this element from natural sources, which were based upon a strict analogy between iodine and 85. Should 85 be present as a branching product in natural radioactivity, its isolation would not offer great difficulties.

In the case of element 43, most of its characters resemble very closely rhenium, and it seems natural to assume that geochemically it would be associated with it and not with manganese. The enrichment process used by Noddack for rhenium should also have concentrated 43. A final separation between these two elements can be performed by distillation in hydrogen chloride current under controlled conditions.

[1] M. Perey, Comptes Rendus **208**, 97 (1939).
[2] C. Perrier and E. Segrè, J. Chem. Phys. **5**, 712 (1937); Nature **143**, 460 (1939).
[3] M. L. Pool and L. L. Quill, Phys. Rev. **53**, 437 (1938).
[4] D. R. Corson, K. R. MacKenzie, and E. Segrè, Phys. Rev. **57**, 459 (1940).

Chemistry III

General Chemical Problems Involving Tracers

Chairman: DR. J. B. CONANT, *Harvard University*

57. Synthesis *in Vitro* of Radioactive Organic Substances. A. K. SOLOMON, *Harvard University, Cambridge, Massachusetts.*

Earliest applications of artificial radioactive tracers to biology made use of the radioactivated atoms in their elementary state, or in the form of some inorganic compound easily derived from that state. Shortly, the necessity of synthesizing more complex organic molecules from the simple radioactive atom became apparent. As is well known, these complex molecules can not be made radioactive by the process of simple bombardment; the recoil of the radioactivated atom usually suffices to break the bond which holds it to the desired molecule.

Synthesis of radioactive organic molecules has as its aim, in common with normal syntheses, the highest possible yield; that is the highest concentration of radioactivity in the synthesized product. The first step towards this goal is the complete separation of the activity from the bombarded target. If the new artificial radioactive element is different than the bombarded element, the problem can usually be solved by ordinary analytical methods. If on the other hand, the new element is isotopic with the bombarded element, these means fail. However, the method of Szilard and Chalmers[1] which takes advantage of the fact that radioactivation means release of the struck atom in a highly reactive state, has been employed with great success.

After concentration which is sometimes combined with one of the succeeding steps, comes the problem of the synthesis itself. For this purpose, radioactivities can be divided into two general classes; those like phosphorus whose long half-life (14.3 days) permits the use of ordinary laboratory methods practically unchanged, and those like carbon whose rapid disappearance (half-life = 20.6 minutes) requires the development of new syntheses in which speed is the most important factor. For example, any step which increases the over-all time of the operation by 20 minutes must justify itself by a twofold increase in yield. To meet these conditions a synthesis[2] has been developed to produce purified lactic acid from raw carbon in one hour and three-quarters.

Other syntheses and general methods are discussed.

[1] Szilard and Chalmers, Nature **134**, 462 (1934).
[2] Cramer and Kistiakowsky, unpublished manuscript.

58. Synthesis *in Vivo* of Organic Molecules Containing Radioactive Carbon. M. D. KAMEN AND S. RUBEN, *Radiation Laboratory and Department of Chemistry, University of California, Berkeley, California.*

Under the conditions of bombardment, radioactive carbon is obtained as CO (ultimately CO_2). Since it is undesirable to dilute the C* excessively with inactive carrier, the quantity of labeled carbon usually amounts to 2 cc or less (S.C.T.P.). If, in addition, the short-lived carbon is used, the investigator is faced with the problem of synthesizing quickly, and in good yields, various organic molecules from a very small quantity of CO_2. Microsyntheses of vital organic material from CO_2 *in vitro* is at a definite disadvantage when compared with *in vivo* methods involving the use of micro-organisms which can be chosen and manipulated to produce quickly and in high yield from CO_2 almost any organic molecule needed as a starting material in metabolic tracer studies. Of course, *in vivo* synthesis also makes possible production of labeled vital principles of unknown composition (i.e., photosynthetic intermediates), a desirable result unattainable by *in vitro* techniques.

To illustrate more definitely the power of the *in vivo* approach, attention may be drawn to some recent studies on the production of acetic acid, propionic acid, succinic acid, methane, etc., from CO_2.[1-3] In experiments with methane bacteria, 40 minutes of exposure to about 2 cc of C^*O_2 resulted in the production of a large fraction of administered C^*O_2 as active methane. *P. pentosaceum* reduced 80 percent of a similar quantity of C^*O_2 in the presence of glycerol to propionic and succinic acids in 30 minutes. *Clostridium acidiurici* in fermenting uric acid reduced appreciable quantities of C^*O_2 in 15 minutes to active acetic acid. Using hypoxanthine as substrate, 80 minutes sufficed to convert nearly all the C^*O_2 to acetic acid. It was found that both methyl and carboxyl groups were labeled.

Photosynthetic organisms can be used for the production of carbohydrates from CO_2. Although hexoses or reducing sugars cannot be synthesized from green algae,[4] it is possible to transform about 20 percent of a given quantity of CO_2 to sugar if barley is used.[5]

The method is seen to be capable of practically unlimited extension to the synthesis of a vast number and variety

of important organic compounds when it is remembered how many micro-organisms with diversified metabolic synthetic processes are available. Further studies on the above-mentioned and other systems will be presented.

[1] Carson and Ruben, Proc. Nat. Acad. Sci. **26**, 422 (1940).
[2] Barker, Ruben and Kamen, Proc. Nat. Acad. Sci. **26**, 426 (1940).
[3] Barker, Ruben and Beck, Proc. Nat. Acad. Sci., August (1940).
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59. The Synthesis of Organic Compounds Containing Stable Isotopes as Tracers. R. SCHOENHEIMER, *College of Physicians and Surgeons, Columbia University, New York, New York.*

This review will be limited to a discussion of such methods as have proved useful in the preparation of substances applicable to biological work.

A. Deuterium

Only compounds with deuterium bound to carbon (methyl, methylene, and methane groups) can be employed for tracer studies. With some exceptions (hydrogen in compounds of low molecular weight, or hydrogen involved in tautomeric equilibrium reactions as in enolisation), such carbon bound hydrogen is "stable." In exceptional cases, namely when the rate of enolisation is very slow, even compounds with deuterium neighboring carbonyl groups may be employed for biological tracer work.

The more commonly employed procedures are:

a. Catalytic hydrogenation with D_2 *of unsaturated compounds in nonpolar solvents or heavy water.*—As the rate of the platinum catalyzed exchange reaction between H_2 and H_2O is considerably slower than that of the hydrogenation of some organic compounds, the hydrogenation with D_2 may be carried out in H_2O as a medium. The resulting compound will have a deuterium content below theoretical. A number of isotopic fatty acids, amino acids, and steroids have been prepared by hydrogenation.

b. Replacement of halogen atoms by deuterium.—Various deutero methanes have been prepared from the corresponding halogen derivatives.

c. Catalytic labilization of carbon bound hydrogen at elevated temperature with D_2SO_4 *or active platinum in heavy water.*—According to Ingold the treatment with concentrated D_2SO_4 of a number of aromatic and hydroaromatic hydrocarbons results in hydrogen exchange. The method has been employed for the preparation of biological fatty acids and amino acids with "stable" deuterium. Aliphatic fatty acids and aliphatic amino acids thereby acquire deuterium only at the alpha-carbon atom. Aromatic amino acids (phenylalanine) also exchange the hydrogen of the ring. Polanyi and Farkas have shown that active platinum or paladium at elevated temperatures may labilize hydrogen of some hydrocarbons. This reaction has now been employed for the preparation of isotopic fatty acids. In the presence of alkali and platinum, aliphatic fatty acids exchange carbon bound hydrogen with that of D_2O. The presence of hydroxyl and amino groups in the compound interferes with the exchange, i.e., the procedure does not seem applicable to alcohols or amino acids.

d. Various methods applicable for the preparation of specific compounds.—(1) decarboxylation in D_2O; (2) hydration of unsaturated compounds, etc.; (3) deuteromethylalcohol, prepared from CO according to Zanetti has been employed by du Vigneaud and collaborators as starting material for methylated compounds (methionine, choline).

e. Biological synthesis.—Animals when given heavy water to drink or plants grown in heavy water synthesise compounds with stably bound deuterium. A large number of such substances have been isolated. The method, while theoretically unlimited is restricted in practice by the cost of heavy water. More economical is the biological conversion of one deutero compound into another.

B. Isotopic nitrogen

Most substances reported were prepared for biological tracer work. They were synthesised with isotopic ammonia as starting material. In view of the value of the isotope the known procedures of amino acid synthesis had to be modified so as to furnish good yields when calculated on the basis of ammonia rather than the carbon chain. The recovery of nitrogen should be quantitative.

Three methods of amino acid synthesis have been employed so far: (a) The phthalimide procedure of Gabriel; (b) the catalytic hydrogenation of keto acids in the presence of ammonia; and (c) the reaction of coumaric acid→hydroxy nicotinic acid→pyridone→piperidone as starting material for ornithine and proline.

Isotopic guanido compounds (arginine, creatine) were obtained with isotopic cyanamide, prepared from cyanogen bromide. Isotopic urea may be prepared by the copper catalysed reaction of diphenylicarbonate with ammonia. Biological synthesis of a large number of compounds has occurred in all experiments when isotopic ammonia or amino acids were given to animals. The isotope content of the newly formed substances is low.

For tracer work it is frequently necessary to employ amino acids with 2 independant isotope markers in one preparation, i.e., deuterium as a tracer for the carbon chain and N^{15} for the amino group. Several such amino acids have been prepared.

60. Production and Properties of Long-Lived Carbon. S. RUBEN AND M. D. KAMEN, *Department of Chemistry and Radiation Laboratory, University of California, Berkeley, California.*

The recently[1,2] discovered long-lived radioactive isotope of carbon has been identified as C^{14}. It has been found that the radiations emitted are low energy negative electrons with an upper energy limit of 145 ± 15 kv. No gamma-rays (<1 percent) could be detected. Two methods of production have been investigated. The first involves the bombardment of carbon by deuterons with high energy deuterons accelerated in the Berkeley cyclotron. The reaction is

$$ {}_6C^{13} + {}_1H^2 \rightarrow {}_6C^{14} + {}_1H^1. $$

The yield at 3 to 4 Mev (saturation energy for thin target activation) is about 3×10^{-6} microcurie per microampere

hour. Using Pollard's estimate for the cross section of this reaction and fitting an Oppenheimer-Phillips curve to the yield data for the $C^{13}(d, p)C^{13}$ reaction at lower energies (0.5 to 2 Mev), it has been possible to calculate a value for the half-life of approximately 1000 years. This can be taken as a lower limit. A sample of the active carbon has shown no appreciable decay (<1 percent) in eight months, placing the half-life value at certainly no less than 25 years. Since the transition from C^{14} to N^{14} by beta-emission appears forbidden from these observations, it is necessary to assume that the ground state of C^{14} possesses several units of angular momentum. This conclusion is not what might have been expected from the analogous case of He^6 decaying to Li^6. The fact that nucleus He^6 exists in an S state would lead on the most straightforward arguments based on present picture of $n-p$ forces to the supposition of a ground state of little or no angular momentum for C^{14}.

The second method of production is based on the disintegration of nitrogen by neutrons, *viz.*:

$$_7N^{14}+n_0{}^1\rightarrow{}_6C^{14}+{}_1H^1.$$

This reaction is exothermic[3] by about 500 kv and so can take place with slow as well as fast neutrons. This process in all probability has a high cross section for slow neutrons. A saturated solution of ammonium nitrate in ten gallons of water when exposed for about six months to neutrons from the 60-inch medical cyclotron at Berkeley yielded a sample of the long-lived carbon, giving about 10^5 counts/min. as measured in a screen-wall counter. The total inactive carbon in which this activity was distributed could be kept lower than one mg. However, ammonium nitrate is not the best material to use from the standpoint of nitrogen and hydrogen content, and moreover there exists the explosion hazard. By using substances such as urea, guanidine, cyanamide, etc., and making full use of the available space around the cyclotron, it should be possible to increase the present yields 100-fold. Such samples, when obtained, will allow dilutions of 100,000-fold without falling below the limit of detectability. The many advantages of neutron activation (i.e., low carrier content, convenience, economy, etc.) indicate it to be the most advantageous method for the production of tracer carbon.

It has been found that nearly all the active carbon can be recovered from the nitrate solution as volatile material (CO_2, CO, and possibly CH_4). Thus, the extraction of the active carbon from large quantities of nitrogenous material can be easily accomplished by pumping off the vapors and subsequent oxidization to CO_2. The nature of the recoil carbon activity in a variety of nitrogen compounds other than nitrate is now being studied to determine the optimum conditions for production of C^{14} by neutron bombardment. It is certain that the shielding of neutron sources can profitably be turned to account by use of nitrogenous compounds which can also produce C^{14} as a by-product of the operation of the apparatus. This is a consideration of some importance in view of the rapidly increasing number of such machines.

C^{14} will be applicable as a tracer in biological studies as is the heavy isotope C^{13} but will be especially useful in researches where high dilution factors are encountered and where it is inexpedient or impossible to use the C^{13}. The technique for detecting the radiations with special reference to elimination of errors due to self-absorption is being developed and a description of the apparatus now in use will be given.

[1] Ruben and Kamen, Phys. Rev. **57**, 549 (1940).
[2] Kamen and Ruben, Phys. Rev. **58**, 194 (1940).
[3] T. W. Bonner and G. Brubaker, Phys. Rev. **49**, 778 (1936).

61. Chemical Effects of Nuclear Transitions. R. S. Halford, W. F. Libby and Don DeVault, *Department of Chemistry, University of California, Berkeley, California.*

The results of many workers taken together show that neutron capture and conversion electron emission both induce dissociation of the molecules in which the radioactive atom is bound. The processes appear to be nearly 100 percent efficient in this respect under all conditions, although reformation reactions usually occur, causing an apparent decrease in the efficiency of ejection. Dilution of a substance undergoing such a process with another which cannot react with the hot ejected fragments results in increase in the fraction ejected to 100 percent in the limit. For example, slow neutron irradiation of CBr_4 in the following various forms gave decreasing percentages of the total induced radioactivity which could not be removed by aqueous extraction: solid CBr_4, 60 percent; 1.2 mole percent solution of CBr_4 in C_2H_5OH, 28 percent; 0.74 mole percent, 13 percent, 0.45 mole percent, 2; 0.06 mole percent, 0.

The problem therefore assumes three phases. One is the existence of thermal interchange between the original substance and the ejected fragments. A second is the nature of the rupture that occurs, e.g. whether ions or free radicals are ejected and the constitution of these fragments. The third is the reactions of these energetic fragments marked with radioactivity with the molecular environment. A rather extensive literature exists on thermal interchanges at present. Results are to be presented indicating a rule that in these violent ruptures the electrons in the bonds broken are distributed among the fragments about as they are thought to be distributed in the bond. For example, ClO_3^- is probably reduced as a result of the ejections following neutron absorption by the Cl, while MnO_4^- quite definitely retains the +7 oxidation number for manganese when it is exposed to slow neutrons.

The reformation reactions appear to obey reasonable rules in view of the high energies of the reacting particles. For example, in the case of the alkyl halides, activity is found in more highly halogenated fractions but the main portion of that which returns to the organic molecules is found to be identical with the original substance, presumably because of the higher probability of energy loss by collision of the excited radioactive halogen atom with another halogen atom of the same mass bound in the molecule. This results in a replacement of the nonradioactive atom by the radioactive one. This process will in general form the new RX* molecule in a somewhat excited state which may allow certain reactions to occur with other

substances which might not occur with the normal unexcited molecules. These reactions may result in the liberation of the radioactive atom, so the effect is a net increase in the extractable halogen radioactivity. Lu and Sugden have shown that aniline accomplishes this effect for organic halides. The generality of the principle is obvious and the applications may prove to be of considerable practical importance in the future. They should result in higher yields of concentrated radioactive materials from neutron irradiations.

Transitions of one nuclear isomer into another, usually by the emission of an internally converted *K*- or *L*-electron, result in efficient ejections also. The mechanism apparently involves partial utilization of the excitation energy of the electronic shells resulting from *K*- or *L*-electron emission and leaves the ejected ions in very reactive states. These transitions may be of use in reaction kinetics because they probably are capable of furnishing atoms at a known rate, each marked radioactively. For example, a solution of $Br^*O_3^-$ with the bromine activity of 4.5 hr. life will have Br^{*-} of 18-min. half-life furnished to it at a constant rate and any reaction occurring in this system involving Br^- should give a product containing 18 min. Br^* providing Br^- and the product do not interchange rapidly thermally.

Biology I

The Study of Animal Metabolism with Radioactive Tracers

Chairman: DR. J. H. MEANS, *Massachusetts General Hospital, Harvard University*

26. Radioactive Iodine as an Indicator in Thyroid Physiology: Observations on Rabbits and on Goiter Patients. SAUL HERTZ, *Massachusetts General Hospital, Boston, Massachusetts.*

This report summarizes a series of cooperative experiments started in the fall of 1937, on the metabolism of iodine in relation to thyroid function. The only radioactive isotope of iodine then available was I^{128}, with a half-period of 26 minutes. The earliest experiments[1] demonstrated that the collection of iodine by the thyroid was extremely rapid, the amount present in the gland within 10 minutes after intravenous injection not being exceeded within 90 minutes. Hyperplastic glands collected more iodine than did normal glands, the injections being equal. A systematic study was then undertaken of the relations among the dosage of administered labeled iodine, the time of collection, previous iodine administration, and the functional state of the thyroid as indicated by its size. The results[2] indicated that the thyroid took up a larger proportion of a small dose of iodine than it did of a large dose. Curves showing these relations were established for normal animals, animals treated with anterior pituitary thyrotropic hormone, animals on an exclusive cabbage diet, and animals injected with methyl cyanide. Previous iodine administration caused a marked decrease in the collection of subsequent doses. When strong samples of the newly discovered long-lived isotopes of iodine became available, further lines of investigation were undertaken. These were the extension of experiments on thyroid iodine collection to patients with Graves' disease, the chemical investigation of the partition of iodine among various iodine fractions in the thyroid, and the introduction of a new technique, multiple labeling,[2] for the study of different doses of iodine at the same time. The multiple labeling technique showed that the collection from a second dose of iodine is almost invariably less than that from the first dose. This led to the suspicion that the routine pre-operative massive iodinization in Graves' disease might be unnecessary. It has now been shown that the response to a single dose is clinically indistinguishable from the response to protracted iodinization. At the same time, a more complete correlation of iodine collection with the known measures of thyroid function, *viz.* basal metabolic rate, thyroid size, histologic appearance, and with the time and method of preparation of the subject was carried out using rabbits. The experiments upon patients with Graves' disease were at first concerned with measuring the amount of iodine in the thyroid (as obtained at operation) which remained from a single initial labeled dose of varying size, administered at various times during the course of iodinization and at varying intervals before operation. In addition, the chemical fate of the iodine was investigated and the urinary excretion followed. As in rabbits, maximum collection was found within a short time after administration, and collection was relatively largest from small doses of iodine. Chemical analysis in the main confirmed previous findings. In a recent series of experiments, an externally placed counter was used to measure the relative activity of labeled iodine in the thyroid as a function of time. By means of a single absolute determination after surgery, it was possible to calculate the absolute content at any previous time. *The initial thyroid collection in previously untreated Graves' disease patients approximates 100 percent for small doses* (0.2–5.0 mg), while the initial collection of previously iodinized patients, normal controls, and the collection of all patients from larger doses is considerably smaller. These results are not inconsistent with the smaller collections obtained by Hamilton and Soley[3] from larger doses. This initially collected iodine rapidly leaves the thyroid in the untreated patients given small doses, less than a third remaining after a week, with a slower decline

thereafter. A series of experiments on the behavior of thyroids isolated and surviving in a perfusion apparatus has been instituted, and it has been shown that the behavior of the thyroid in collecting iodine from the perfusion fluid is directly comparable to the results *in vivo*.

[1] Hertz, Roberts and Evans, Proc. Soc. Exp. Biol. Med. **38**, 510 (1938).
[2] Hertz, Roberts, Means and Evans, Am. J. Physiol. **128**, 568 (1940)
[3] Hamilton and Soley, Am. J. Physiol. **127**, 557 (1939).

27. Distribution of Radio-Iodine in Normal Rabbits. H. C. HODGE, W. MANN AND I. ARIEL, *University of Rochester, School of Medicine, Rochester, New York.*

Following intravenous injection of radioactive iodine, there is an immediate distribution to the various tissues from the blood with considerable fluctuation in the relative amounts found at the various periods observed. The thyroid takes up a relatively large percentage of the injected dose. The radio-iodine appears promptly in the urine. Up to 30 percent of the dose may be excreted in nine hours. The lung and kidney tissue contain relatively high percentages of the radio-iodine dose; liver, spleen, heart, bile, and submaxillary gland contain intermediate amounts; and muscle, skin, diaphragm, and testicle have low percentages.

28. Studies in Physiology of Normal and Diseased Thyroids of Human Beings by the Use of Radioactive Iodine. JOSEPH G. HAMILTON AND MAYO H. SOLEY, *William H. Crocker Radiation Laboratory, University of California, Berkeley, California and the University of California Medical School, San Francisco, California.*

A radioactive isotope of iodine (I^{131}) has been used as tracer to study various phases of iodine metabolism in normal subjects and in patients with thyroid diseases. The rapid absorption and excretion of iodine has been confirmed. Toxic goiters in 16 patients who had received previously large amounts of ordinary iodine were able to take up considerable quantities of radio-iodine, but less than the nontoxic goiters in 8 patients who had not received iodine prior to these experiments. Radio-iodine was given to 2 patients with carcinoma of the thyroid and it was observed that the cancerous tissue did not have the ability to accumulate more than small traces of this element.

The iodine metabolism of the thyroid glands of normal subjects and of patients with several types of thyroid disorders (who had received no iodine previously) was studied in the intact individuals following the oral administration of radio-iodine. A Geiger-Müller counter was placed over the thyroid gland and the amount of accumulated radio-iodine was determined by the measurement of the gamma-rays emitted from the gland. This procedure revealed that the thyroids of 5 normal subjects, of 2 patients with nontoxic goiters, of 10 patients with toxic goiters, and of 4 patients with hypothyroidism but no goiters, concentrated and released iodine in a characteristic manner for each condition described. The thyroids of the normal individuals stored the radio-iodine slowly, the maximum uptake of from 1 to 5.5 percent (average of 4.5 percent) was observed at the end of 48 hours, but these thyroids retained over 80 percent of their accumulated radio-iodine at the end of 30 days. A similar pattern was observed in the thyroids of the patients with nontoxic goiters, but these glands took up more than twice the amounts stored in the thyroids of the normal subjects. The thyroids of the patients with toxic goiters took up the radio-iodine very rapidly so that the maximum uptake of from 7 to 30 percent (average of 14 percent) occurred at from 1 to 4 hours after administration. At the end of 24 hours the content of radio-iodine in these glands diminished to the extent of one-half to one-fifth of the maximum uptake. Thereafter the loss of radio-iodine from the glands was much less, but was greater than was observed in the normal subjects and the patients with nontoxic goiters. The thyroids of the patients with hypothyroidism had a limited capacity to accumulate the administered radio-iodine; the uptake in these patients at the end of 48 hours ranged from 0.02 to 0.08 percent (average of 0.05 percent).

Radio-iodine has been employed to investigate the relationship between the deposition of radio-iodine in thyroid tissue and its histological structure. Two days following the administration of the radio-iodine the thyroids were removed and thin sections prepared from the glands. These sections were placed against photographic films and after a suitable period of exposure the films were removed and developed, and the sections were stained. The areas of darkening on the films, which were produced by the action of the radio-iodine beta-particles, indicated the regions of the sections in which the largest accumulations of radio-iodine had taken place. The sections and their corresponding radio-autographs were compared under a microscope in order to correlate the deposition of the radio-iodine with the microscopic anatomy of the thyroid tissue. Thyroids from patients with toxic goiters, nontoxic goiters and carcinomas of the thyroid were studied by this technique. The results of these studies indicated that the radio-iodine was stored predominantly in those areas of the thyroid in which the greatest degree of functional activity appeared to be. The cancerous thyroid tissue had no demonstrable ability to accumulate the administered radio-iodine.

A comparison of the uptake of radio-iodine and element 85 (eka-iodine) by normal and hyperplastic thyroids of guinea pigs revealed that this newly discovered halogen is taken up by these glands in a manner similar to iodine. The rates of excretion of these two halogens were observed to be almost identical. A single experiment with element 85 administered to a patient with a nontoxic goiter revealed that approximately 10 percent was accumulated in the gland at the end of 24 hours and the uptake curve was similar to that of radio-iodine.

29. The Use of Radioactive Iron in the Study of Problems of Iron Metabolism and Experimental Anemia. P. F. HAHN AND G. H. WHIPPLE, *University of Rochester, School of Medicine and Dentistry, Rochester, New York.*

There are many opportunities for the employment of the artificially radioactive isotope of iron and studies have been

carried out in the following fields: (1) The factors involved in the regulation of absorption of iron with especial attention to the mechanism regulating the acceptance or refusal of iron when administered orally; (2) the amount of iron excretion and the pathway of this process; (3) the factors governing the rate of uptake of iron by the immature red blood cell and the state of maturation at which the iron is incorporated in the cell; (4) the means of transport of iron in the body and the form in which the element occurs in combination during transport; (5) the proof of the existence of iron in the form of hemoglobin in the red blood cell within a few hours following the administration of the radioactive isotope by mouth; (6) the lack of exchange of iron in the plasma with iron of the hemoglobin molecule as a purely physico-chemical exchange reaction; (7) the distribution of iron in the various tissues following its oral and parenteral administration; (8) the origin of iron in the bile and the factors regulating the amount of secretion by this route; (9) the rate of turnover of iron in the metabolism of muscle hemoglobin iron; (10) the use of radioactive iron as a means of tagging hemoglobin and red blood cells in the study of the volume of red blood cells in circulation and the total volume of red cells in the vascular system.

Other possibilities are presented such as the study of the respiratory enzymes containing iron (e.g. cytochrome) but the studies of these substances would be better deferred until higher potencies of the isotope are available. The various fields of clinical research in the anemias and numerous diseases involving dyscrasias of iron metabolism have been approached but further information awaits the use of the isotope among a wider variety of controlled experiments which in turn depend on the availability of large amounts of the radioactive material.

It has been demonstrated that the anemic animal deficient in iron stores will absorb considerably larger amounts of iron than the normal animal. The mechanism of this unusual physiological reaction has been studied from a number of angles. Among the most enlightening experiments was one in which a normal animal was shown to have absorbed only 1.3 percent of the dose of 130 mg of iron containing the radioactive isotope. When this animal was rendered acutely anemic by the removal of about two-thirds of its total circulating blood during the course of a few hours, and twenty-four hours later given the same dose of radioactive iron, the amount of absorption was about the same as before, within experimental limits. After being allowed to return to a near normal range of circulating hemoglobin at the expense of the body stores of iron, and again fed radioactive iron at about the same dosage level, the amount of absorption was 10 percent instead of less than 2 percent. This would suggest that the level of anemia *per se* did not influence the amount of the metal absorbed but that rather the amount of tissue iron, probably one of the iron fractions of the mucosa, was the determining factor.

The question as to the site of iron absorption is of considerable interest. It has been possible to show by means of an anemic dog with a complete gastric fistula that considerable absorption of the iron containing the radioactive isotope takes place in the stomach, in fact, as much was absorbed from such a pouch during a two-hour instillation period as one might expect from the oral administration of the same amount of iron to a standard depleted anemic dog.

Experiments are in progress to determine whether the amount of absorption in such an intact pouch may be altered by the maintenance of a high level of tissue iron. It is also being investigated whether a dog with a low level of tissue iron but a normal blood picture in every respect (normal saturation of hemoglobin in red cells and normal plasma iron) will absorb iron as well as a depleted anemic animal.

It is felt that a number of fundamental processes underlying the metabolism of iron may be much better understood by the continued use of the radioactive isotope in these and similar studies.

30. Studies with Radioactive Copper.* M. O. SCHULTZE AND S. J. SIMMONS, *Departments of Chemistry and Physics, University of Pittsburgh, Pittsburgh, Pennsylvania.*

Physiological studies with radioactive copper require material with a very high radioactivity and a low content of total copper because (1) radioactive copper has a short half-life (12.8 hours), (2) very small amounts of copper elicit a physiological response, and (3) copper is toxic in large doses.

With radioactive copper prepared by bombardment of nickel with protons these requirements can be met. Some of the samples at our disposal yielded an activity of 2 million counts per minute per mg of total copper 48 hours after bombardment, as measured in the form of a copper sulfate solution by a dipping counter.

Radioactive copper was fed to anemic copper deficient and iron deficient rats. After 24 or 48 hours the distribution of the copper in various tissues and organs was studied. From 100–200 micrograms of total copper fed only 3–7 pcercent were retained in the tissues (excluding the gastrointestinal tract). The tissues of anemic copper deficient rats retained more copper than those of anemic iron deficient rats. The kidneys and the liver had the highest concentrations of retained copper. A small fraction of the copper was found in the bone marrow of the copper deficient rats. This is of special interest in relation to blood formation because marked changes in enzyme activity associated with hematopoietic activity of the bone marrow have been demonstrated as early as 24 hours after copper therapy of deficient rats.

Copper can be extracted quantitatively from aqueous solutions by converting it into the copper complex of diphenylthiocarbazone (dithizone) which is soluble in carbontetrachloride. This reaction was used for the isolation of the copper from solutions of the bombarded nickel and of ashed animal tissues prior to counting the activity in a Geiger-Müller counter. It also permitted concentration of the radioactivity in small volumes, aliquots of which were used for counting.

* The cooperation of the Department of Physics, University of Rochester, Rochester, New York, is gratefully acknowledged.

Biology II

The Study of Animal Metabolism with Radioactive Tracers

Chairman: Dr. J. C. Aub, *Collis P. Huntington Memorial Hospital, Harvard University*

40. The Permeability of Cells to Cations. Waldo E. Cohn, *Collis P. Huntington Memorial Hospital of Harvard University, Boston, Massachusetts.*

The radioactive isotopes of sodium and potassium afford a direct method for measuring the permeability of cells to these ions. After intravenous injection of Na^{24} or K^{42}, in the form of the chloride, the radioactive isotope disappears rapidly from the plasma, reaching a relatively constant low level in an hour or two. This then falls but slowly. From a study of such curves, coupled with direct analyses of certain tissues, information can be obtained as to the relative permeability of the tissues of various animals to these cations.

From such a study in normal dogs, it appears that injected Na^{24} distributes itself uniformly throughout extracellular water within 100 minutes. No appreciable amount enters the intracellular phase, with the exception of the erythrocytes. These undergo a slow exchange of sodium ions with the plasma, requiring about a half-day for 50 percent completion of the process. The rate of this exchange seems to be proportional to the difference between the plasma and erythrocyte Na^{24} concentrations.

After the intravenous injection of $K^{42}Cl$ into dogs, the plasma radioactivity falls more rapidly than is the case with Na^{24}, and reaches a lower plateau concentration in 60 to 100 minutes. From the value of this concentration it can be calculated that only 4 percent to 4½ percent of the injected K^{42} is then present in the extracellular phase. The remainder (less that excreted) must be present in the intracellular phase at a concentration 10 to 12 times that in the plasma. This represents about a 40 percent exchange of intracellular K within this time. After this rapid exchange, there seems to be a secondary slow exchange requiring two or three days to approach completion. The erythrocyte K is apparently exchanged in a similar manner.

Intraperitoneal or oral administration of these isotopes to rats leads to conclusions that are qualitatively the same but quantitatively different. The distribution of Na^{24} throughout the various tissues conforms to that expected from the amount of extracellular water in each. There is no storage of orally-administered Na^{24} by the liver, as is the case with K^{42}. The rate of entry of K^{42} into muscle cells and erythrocytes is apparently much lower than that observed in dogs, and the initial rapid entry of K^{42} seems to be lacking. At the end of four hours, the exchange of muscle *K* seems to be only 4 percent completed. These relatively slow exchanges are comparable to those observed in rabbits by other investigators.

Experiments on human subjects lead to the tentative conclusion that tissue cell and erythrocyte exchange of K is here also a relatively slow process. Small exchanges within the first few minutes are noted, and within two hours the intracellular K^{42} concentration is 3 to 5 times that in the extracellular phase, representing a 10 to 20 percent exchange of K. As time goes on, this seems to rise slowly. The erythrocytes at first behave as though the K^{42} is evenly distributed throughout all the water of the blood. Although human red blood cells contain much more K than those of the dog, these results are quite similar to those obtained on the latter.

These results, in conjunction with those of other investigators, make it apparent that the peculiar distribution of cations between intra- and extracellular fluids cannot be ascribed to the classical semipermeable membrane. Whatever mechanism is postulated must permit an exchange of cations between intra- and extracellular fluids.

41. The Distribution of Radioactive Potassium, Sodium and Chlorine in Rats and Rabbits. Wallace O. Fenn, *University of Rochester, School of Medicine and Dentistry, Rochester, New York.*

The animals were killed at various times after injection and the tissues were sampled. The samples were dissolved in concentrated nitric acid. After measuring the radioactivity the same solutions were analyzed chemically for the element concerned.

The potassium experiments were performed by Dr. T. R. Noonan and the author with the collaboration of Miss L. Haege. From the results calculations were made of the tissue of plasma "activity" (percent of injected counts per gram) and of tissue or plasma "potassium activity" (percent of injected counts per millimol of potassium).

The potassium activity in the plasma rises rapidly to a maximum and then falls asymptotically to a low level indicating complete mixing.

The tissues may be classified according to their behavior into two groups. The first group, consisting of liver, gastrointestinal tract, kidney and heart, shows a rise and subsequent fall of potassium activity similar to that of plasma but with the peak delayed to varying degrees. A result similar to this would be expected as a result of rapid exchange of radioactive potassium for normal potassium. The second group consists of skin, muscle, testes, brain and red cells. In this group the rate of exchange is so slow that the potassium merely rises slowly to a maximum value equal to the final low level reached in the plasma at the time of complete mixing (4 to 10 hours). The results could also be explained by a mass movement (without exchange) of highly active potassium if that movement were greater into the tissues of the first group than into those of the second group. There is evidence of a difference of this sort between liver and muscle. It is impossible from the present data to distinguish between mass movement and exchange as factors in this experiment, but both are certainly involved.

Stimulated muscles of rats take up radioactive potassium more rapidly than resting muscles, but this is probably due to an increased circulation because the same acceleration is found on merely denervating a muscle and because isolated frog muscles stimulated in Ringer's solution do not show this effect.

Rat red blood cells *in vivo* exchange 55 percent of their K in 10 hours and 79 percent in 18 hours. Human cells *in vitro* exchange 12–14 percent in 10 hours. Without evaluating the thickness and the surface area of the membranes a pseudo-diffusion coefficient can be calculated. Values in min.$^{-1}$ of 0.2 to 0.25×10^{-3} for human, 0.32 to 0.66×10^{-3} for rabbits and 1×10^{-3} for rats were calculated.[1]

Using rats and rabbits injected with radioactive Na or Cl, Dr. Jeanne Manery with the cooperation of Dr. Bale has compared the tissue to plasma ratio of Na and Cl determined by chemical analysis with the same ratios for Na^{24} or Cl^{38} determined by the radioactivity. The time necessary for the Na^{24} or Cl^{38} ratio to reach the corresponding ratio for the normal isotopes is taken as a measure of the rate of penetration. In most tissues penetration of Na^{24} was complete in 1 hour and nearly complete in 8–15 min., but was delayed in brain, testes and femur. Likewise radioactive chloride completely exchanged with normal Cl within 8–10 min. in most tissues of both rats and rabbits. In testes both Na^{24} and Cl^{38} penetrate quickly only about 20 percent of the tissue (presumably extracellular space) while the usual Na space is 30 percent and the usual chloride space is 45–50 percent.

[1] See Dean, Noonan, Haege and Fenn, J. Gen. Physiol., in press.

42. The Use of Radio-Sodium and Radio-Potassium in the Study of Adrenal Physiology. EVELYN ANDERSON, MICHAEL JOSEPH AND HERBERT M. EVANS, *Institute of Experimental Biology and the Division of Medicine, University of California, Berkeley and San Francisco, California.*

The role of sodium and potassium in the physiological mechanisms of the adrenal cortex is still obscure, as is also our understanding of the essential function of this endocrine gland. Two very important facts on the relation of sodium and potassium metabolism to adrenal cortical physiology have been well established in the last few years, namely: (1) that the removal of the adrenal gland causes a lowering of the sodium and an increase of the potassium levels in the blood serum, which is associated with a wastage of sodium in the urine and a retention of potassium by the kidney; and (2) that the administration of sodium chloride to adrenalectomized animals considerably delays the onset of adrenal insufficiency. The first of these observations has been extended recently by Harrison and Darrow who have shown that the selective reabsorption of sodium and potassium by the kidney tubule is seriously impaired in the adrenalectomized animal.

The use of radio-sodium and radio-potassium has greatly facilitated the investigation of the relation of these two electrolytes to the function of the adrenal cortex. We have been able to confirm observations (1) and (2) as stated above and also to extend these findings. A summary of our studies shows the following:

1. Adrenalectomized rats fed a standard diet and given tap water to drink show an increased rate of excretion of administered radio-sodium and a diminished rate of excretion of radio-potassium. The rate of excretion of these "tagged" electrolytes can be correlated with the excretion of body sodium and potassium. The giving of a 1 percent sodium chloride solution to adrenalectomized rats instead of tap water to drink corrects the wastage of sodium and the retention of potassium so that these animals excrete the electrolytes in the same proportion as normal animals.

2. Removal of the posterior lobe of the pituitary in adrenalectomized rats also prevents the wastage of sodium.

3. Rats which have been reared on a low sodium diet excrete radio-sodium more rapidly than normal rats and retain radio-potassium in greater amounts than normal. In this respect they resemble untreated adrenalectomized rats. Rats reared on a low potassium diet excrete radio-sodium at a normal rate, but retain radio-potassium.

4. In the first 24-hour period after operation, adrenalectomized rats show a significant increase in the rate of excretion of an administered dose of radio-sodium and a retention of radio-potassium. This early change in electrolyte excretion is accompanied by changes in carbohydrate metabolism.

5. Rats will survive and continue to grow for several months after adrenalectomy without hormone therapy provided an "optimum" amount of sodium chloride is given. The animals so treated at first excrete the administered radio-sodium at the same rate as normal animals, but later they show sodium retention which is in marked contrast to the sodium wastage of untreated adrenalectomized rats. The excretion rate of radio-potassium is the same in these animals as in the normals.

6. The administration of adrenal cortical hormone to normal rats causes a retention of radio-sodium and an increased excretion of radio-potassium. A given dose of adrenal cortical hormone causes an increased excretion of radio-potassium to a more pronounced degree in the partially depancreatized rat than in the normal animal.

43. The Intake of Radioactive Sodium and Potassium Chloride and the Testing of Enteric Coatings. K. LARK-HOROVITZ, *Department of Physics, Purdue University, Lafayette, Indiana.*

The intake of radioactive NaCl and KCl has been measured[1] using the activity measured in the hand as an indicator. The salts have been administered orally in aqueous solution or in a soluble capsule to study the intake from the stomach and by using capsules with enteric coatings for absorption through the intestines. For comparison the salts have also been injected and the intake from aqueous solutions applied to the skin and mucous membranes has been studied. The absorption in the stomach detected after two minutes in the hand shows a steady rise, reaching a constant level in a few hours which is kept for over thirty hours as already observed by others.

Using two counters simultaneously, one to measure the activity in the hand as indicator for the appearance of the salts in the body and one to follow the capsule containing

the salt on its way through the digestive organs, we can decide whether the capsule dissolves in the stomach, develops a leak, letting the salt slowly escape, or whether it breaks in the small intestines. In this way it is possible to locate the capsule on its way through the intestines quite definitely, to test the efficacy of the enteric coating, and to observe the difference in behavior when the salt is taken up from either the stomach or the small intestines. If taken up from the intestines, the measurements in the hand indicate a strong initial absorption marked by a temporary rise of the sodium level in the blood stream which is equalized again by back diffusion. This temporary rise is similar to the one observed after injecting the salt, in which case the back diffusion is indicated by a strong activity of the gastric juice.

For a quantitative evaluation of the measurements in the hand these have been compared with the activity of blood samples taken at different intervals either from the finger tips or from the vein. It has been found that the amount of sodium, potassium, and chlorine found in the blood increases with increasing dosage of the salt taken. While the rate of intake obtained from the measurements of the blood samples is similar to the one observed in the hand, the amount of salt found in the blood indicates a different mechanism of intake for Na and K. Assuming a total blood volume of 4 to 5 liters, the total amount of labeled Na and Cl found in the blood is much larger than one would expect if all the Na and Cl in blood, tissues, bones, and muscles could be freely exchanged; the K content of the blood on the other hand is much smaller than to be expected. In agreement with those observations, the activity measured in the hand after the intake of K corresponds to a larger blood equivalent than in the case of Na and the absorption takes place much more slowly. Most of the K activity in the hand must be due to the uptake of labeled ions in the tissues, bones, and skin.

To distinguish between the uptake in the serum and the blood corpuscles, the blood samples taken from the vein have been centrifuged and the activity of the separates determined. The ratio of labeled ions in serum and cells shows that while over 80 percent of the sodium content of the red cells can be exchanged, only 10 percent of the potassium can be replaced. These values have been reached both for the intake of salts from the stomach and from injections. With the activities used so far an uptake from aqueous solutions by the skin and mucous membrane directly has not been found.[2]

[1] These experiments have been carried out during the last few months with H. Leng (now A.A.U.W. Research Fellow for 1940–41 at Purdue University).

[2] Recent experiments by Johnson and Leng at Purdue University have shown that a definite intake of Na takes place through the skin from ointments with a lanolin base.

44. Tracer Studies with Radioactive Isotopes of the Metabolism of Calcium and Manganese in the Animal Organism. DAVID M. GREENBERG, *Division of Biochemistry, University of California Medical School, Berkeley, California.*

Calcium.—The preparation of labeled calcium salts will be described. The essential procedure is to scrape off the active portion of the calcium target, free it, from contaminating radioactive scandium and then by repeated precipitations as the oxalate and ignition obtain the calcium as the carbonate from which it is readily converted to any desired salt.

Measurements of the very soft β-radiation of calcium have been carried out with the Libby screen wall counter tube. This gives very accurate results, but is time consuming.

The subject of biological study has been the absorption, excretion, and distribution of orally administered calcium by the normal rat. Differences in the metabolic picture when the chloride, lactate, and gluconate of calcium are employed will be brought out. More than 90 percent of the retained calcium is stored in the bone and teeth. This distribution of the labeled calcium in the different structures of the bone and the teeth will be pointed out.

Manganese.—Radioactive manganese Mn^{54} of fairly high specific activity was obtained from iron bombarded in the cyclotron by separating it from radioactive iron, cobalt, and other impurities. The radioactivity of the manganese in the biological material can be suitably measured with a metal wall counter tube.

The results obtained show that radioactive manganese, Mn^{54} is suitable for "tracer" studies on the metabolism of manganese.

On a normal diet, manganese is very poorly retained by the rat. Over 90 percent of a one mg dose was excreted when administered either by stomach tube or by intraperitoneal injection. There is a preferential excretion via the intestines, only a trace is excreted in the urine.

Liver, bone, and muscle take up appreciable quantities of the absorbed manganese.

The results of a comparison study of the manganese metabolism of normal chicks and chicks suffering from perosis will be described.

45. Biological Investigations with Radioactive Calcium and Radioactive Strontium. Simultaneous Production of a Radio-Strontium for Therapeutic Bone Irradiation and a Radio-Yttrium Suitable for Metallic Radiography. CHARLES PECHER, *William H. Crocker Radiation Laboratory, University of California, Berkeley, California.*

Radioactive Ca^{45} and Sr^{89}, produced by the bombardment of calcium and strontium with 16 million-volt deuterons of the Berkeley 60-inch cyclotron have been used as tracers for mineral metabolism studies. The low yield of Ca^{45} and the softness of its beta-rays compells the use of a screen-wall counter as detector. The yield of Sr^{89} is high, and its beta-radiation is easily measured with an electroscope.

When a tracer dose of radio-calcium lactate is injected intravenously to mice, 45 to 70 percent (average: 58 percent in 30 mice) of the dose is recovered in the skeleton after 20 hours. When the dose is given orally, 13 to 30 percent is recovered in the bones. The activity of the soft tissues is negligible. 33 percent (average of 35 mice) of a tracer dose of radio-strontium lactate when administered intravenously

and 11 percent (average of 25 mice) when administered orally is retained in the bones of adult mice 20 hours after administration. The excretion of the radio-strontium during the first day is larger than that for radio-calcium, but the distribution of the activity among the different tissues is almost the same for Ca* and Sr*. Uptake of both radio-calcium and radio-strontium is highest in the trabecular bone, lowest in the liver and fat. Table I compares the

TABLE I. *Percent of dose per gram wet weight.*

	BONE	MUSCLE	SKIN AND HAIR	DIG. TRACT	LIVER
Ca^{45}	22	0.33	0.20	0.36	0.12
Sr^{89}	12	0.17	0.15	0.23	0.07
P^{32}	5.2	1.4	0.75	1.3	2.1

activities of some tissues 24 hours after intravenous administration of three radioactive agents.

Tracer doses of radio-calcium and radio-strontium, administered intravenously to mice, are excreted both in the urine and feces—generally more in the feces.

Uptake in the bones of the chloride, lactate and gluconate of strontium has been compared when the dose is injected intravenously and when it is introduced into the stomach. In a group of 60 mice, the uptake has been found to be independent of the anion for both ways of administration.

Calcium metabolism during pregnancy.—In mice, a large fraction (5 to 25 percent) of the radio-calcium (or radio-strontium) previously fixed on the mother's bone migrates to the foetus during the last days of the pregnancy and to the milk during the first days of the lactation period.

The specific activity of the calcium in the whole body of the newborn mice is higher (1.1×10^{-2} the specific activity of the injected solution) than the specific activity of the mother's bone (0.67×10^{-2}), although the activity of the newborn mice issues from the mother's bone. So it appears that the last calcium fixed on the mother's bone is the first to be removed.

When radio-strontium is given intravenously to mothers during the lactation period, a large fraction of the dose (20 percent) is recovered in the offspring after two days. The excretion of radio-strontium in the milk of two cows intravenously injected with radio-strontium lactate has been studied by Dr. Erf and the writer. 7.9 and 10.0 percent of the injected dose have been recovered in the milk during the four days following the injection.

The selective fixation of radio-strontium on the bones, its ease of production, the suitable energy of its beta-rays (1.5×10^{6} ev), its convenient half-life (55 days), the innocuousness of small doses of strontium, have suggested its use as a specific method of irradiation of the skeleton. (Applicable in multiple myelomas, giant cell tumors, polycythemia, some metastatic bone tumors, etc.)

The first clinical experiments have been started by John H. Lawrence and the writer.

Incidentally, there was found as a secondary product in the preparation of radio-strontium a large amount (13 milligrams radium equivalent per 1000 microampere hours deuteron bombardment) of long life (100 days) radio-yttrium (Y^{86}). It emits a penetrating gamma-radiation nearly identical to radium gamma-radiation and may be used instead of radium as a gamma-ray source. It has produced successful metallic radiography.

* Fellow of the Belgian-American Education Foundation.

Biology III

The Study of Animal Metabolism with Radioactive Tracers

Chairman: DR. J. G. HAMILTON, *University of California*

65. The Use of Radioactive Tracers in Biological Investigations. GEORGE HEVESY, *Copenhagen.*

Read by title.

66. The Phospholipid Activity of the Liver as Measured with Radioactive Phosphorus. I. PERLMAN AND I. L. CHAIKOFF, *Division of Physiology of the Medical School, University of California, Berkeley, California.*

The problem of fatty livers has received considerable attention both experimentally and clinically. Thus far, however, little success has been attained in arriving at an explanation for their production or cure. Attempts have been made to obtain insight into the mechanism of fat mobilization to and from the liver by analyzing the lipid constituents of normal and fatty livers. The results of such investigations have shown that the lipid composition of normal and fatty livers usually differs only in its levels of triglycerides. Relevant to the present study is the fact that the total phospholipid content remains relatively constant when a liver goes through a cycle from the normal to fatty and back to normal state.

Recent studies from this laboratory have shown that under the conditions investigated the level of liver fat depends upon the rate of phospholipid turnover. Since the total quantity of phospholipid remains relatively static this could only be shown by labeling the newly-formed phospholipid molecules, in this case, with radioactive phosphorus. It was found in general that the *administration of a substance which prevents or cures fatty livers in rats results in an accelerated phospholipid turnover.* Cholesterol feeding, on the other hand, which accentuates the production of fatty livers, depresses the phospholipid turnover in the liver.

The above conclusions were based on the following experiments:

Choline.—Rats maintained for several days on a high fat and low protein diet received radioactive Na_2HPO_4 as a labeling agent and the effect of choline administration upon the turnover of phospholipid was determined at several intervals. Livers removed 1 hour after choline administration had the same *labeled* phospholipid content as those from rats which received radioactive phosphorus but no choline.[1] At the 3- and 6-hour intervals the phospholipid activity of choline-treated rats exceeds that of the controls by 30–40 percent but by 12 hours this effect of a single administration of choline had largely disappeared. It was also observed that a graded increase in phospholipid turnover results from successively increasing the amount of choline administered.

Betaine.—Experiments of the same type were carried out with the betaine of glycine. Qualitatively the results were similar to those of choline but whereas 10 mg of choline chloride produced a definite acceleration of phospholipid turnover, over 50 mg of betaine chloride were necessary to produce a comparable effect.[2] This is in keeping with the relative lipotropic activities of choline and betaine.

Amino acids.—In keeping with its lipotropic action, methionine produced an elevation in phospholipid turnover of the liver.[3] Of all the other amino acids investigated only cystine and cysteine behaved similarly. Glycine, alanine, tyrosine, glutamic acid, asparagine, proline, serine, as well as creatine, sarcosine, taurin and di-β-hydroxyethyl sulfoxide had no effect.[4]

Cholesterol.—When a few hundred mg of cholesterol were ingested along with butter over a 30-hour period, the level of newly-formed phospholipid in the liver was depressed.[5] This may be a factor in the production of fatty livers by cholesterol. Choline administration to cholesterol-treated rats resulted in a marked increase in the phospholipid turnover.

Summary.—With the aid of radioactive phosphorus it has been found possible to measure the phospholipid activity of the liver under a variety of experimental conditions. A theory is presented which indicates that one of the factors involved in the fat balance of the liver is the phospholipid turnover. If an increased phospholipid turnover is induced (other factors remaining constant) the lipid content of a fatty liver is reduced.

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[4] I. Perlman, N. Stillman and I. L. Chaikoff, J. Biol. Chem. (in press).
[5] I. Perlman and I. L. Chaikoff, J. Biol. Chem. **128**, 735 (1939).

67. Phospholipid Metabolism Studies Using Radioactive Phosphorus. FRANCES L. HAVEN, *Department of Biochemistry and Pharmacology, School of Medicine and Dentistry, The University of Rochester, Rochester, New York; and the National Cancer Institute of the United States Public Health Service.*

The two biological tracers which have been the most widely used in studies of phospholipid metabolism are elaidic acid and radioactive phosphorus. Since elaidic acid is a solid unsaturated fatty acid while most solid fatty acids are saturated, it can be traced among the fatty acids of the phospholipids and in this way serves as a marker. By feeding elaidin, Sinclair found that the rate of turnover of elaidic acid was rapid in the liver phospholipids and slow in the muscle phospholipids. Similar results on the phospholipids of these tissues were obtained by Chaikoff and by Haven using radioactive phosphorus.

Phospholipids are essential constituents of tumor cells, being more abundant in malignant than in benign tumors. By feeding elaidin to rats bearing Carcinosarcoma 256 Haven found that the tumor phospholipids resembled muscle rather than liver phospholipids in their rate of turnover. However, when radioactive phosphorus was used to study the phospholipid metabolism of this tumor, the rate of turnover was found to resemble the rapid rate of liver phospholipid rather than the slow rate of muscle phospholipid. Sinclair has recently pointed out that kidney phospholipid shows a similar difference in rate of turnover as measured by him using elaidic acid (slow turnover), and as measured by Artom and co-workers and by Chaikoff and co-workers using radioactive phosphorus (rapid turnover). These divergent results obtained by the use of the two indicators seem to show that phospholipids may have at least two different functions, one concerned with fatty acid, the other with phosphoric acid metabolism.

Radioactive phosphorus has also been used to measure the rate of turnover of the individual phospholipids, lecithin and cephalin, of Carcinosarcoma 256. Rats bearing this tumor were killed from four hours to twenty days after receiving by stomach tube a solution of disodium hydrogen phosphate containing radioactive phosphorus. Tumor phospholipids were isolated and the lecithin and cephalin fractions separated by means of absolute alcohol. The degree of separation was measured by choline determinations on the total mixed phospholipid and on the lecithin fractions. The radioactivity of the lecithin fraction expressed as percentage of dose per gram of phospholipid was greater even at four hours than that of the cephalin fraction. While the activity of each fraction increased with time, that of the lecithin fraction did so at a faster rate than that of the cephalin fraction until the peak in activity was reached at 24–30 hours. After this the activity of the lecithin fraction decreased while that of the cephalin fraction continued to increase, reaching its peak at 40 hours. The activity of each fraction then decreased at approximately the same rate. The faster rate of turnover of the lecithin fraction of the tumor constitutes a further resemblance between the phospholipids of this tumor and those of liver. Moreover, it may mean that cephalin is formed from lecithin.

68. Radio-Phosphorus Studies in the Chemistry of Anaerobic Muscular Contraction. JACOB SACKS, *Laboratory of Pharmacology, University of Michigan, Ann Arbor, Michigan.*

In contraction of striated muscle under anaerobic conditions, the principal chemical reaction is the formation of lactic acid from glycogen. There is associated with this a decrease in the amount of phosphocreatine; part of the phosphate thus lost is found as inorganic phosphate, and

part as hexosemonophosphate. There is usually no change in the quantity of adenosine triphosphate.

Studies of the enzyme systems present in cell-free muscle extracts have resulted in an interpretation of the chemistry of anaerobic contraction which considers that the phosphate changes are associated with the formation of lactic acid. According to this formulation, generally known as the Embden-Meyerhof schema, lactic acid is formed by a complex series of reactions which involves interchanges of phosphate groups between all these compounds and various others which appear as intermediates.

From studies of the reactions taking place in the contracting muscles themselves, a different formulation has been developed. In this it is postulated that the formation of lactic acid is independent of reactions involving the phosphorus compounds. This formulation regards the hydrolysis of phosphocreatine as serving primarily as a source of alkali to neutralize the lactic acid formed, and considers that the formation of hexosemonophosphate is a supplementary reaction in contraction, rather than an intermediate one in the formation of lactic acid.

Radio-phosphorus offers the possibility of determining whether the formation of lactic acid does involve the postulated interchanges. If a differential distribution of radio-phosphorus among the four compounds of muscle can be obtained in the animal body, the changes in this distribution which accompany the formation of lactic acid in contraction will establish whether the interchanges do take place.

Using cats under amytal anesthesia, it was found that radio-phosphorus, injected as Na_2HPO_4, underwent such a differential distribution. The inorganic phosphate of the resting muscle had ten times the relative radioactivity of the phosphocreatine P. The relative radioactivities of the adenosine triphosphate and hexosemonophosphate P were even lower than that of the phosphocreatine P.

In companion muscles stimulated so as to produce large amounts of lactic acid, the differential distribution of the radio-phosphorus was retained. The observed distribution was that which would be anticipated if the only reactions involving phosphate compounds which took place were the hydrolysis of some phosphocreatine and the conversion of an additional amount to hexosemonophosphate. There was no evidence of participation of phosphocreatine, adenosine triphosphate or hexosemonophosphate in the formation of lactic acid.

From this it is concluded that the Embden-Meyerhof schema does not represent the mechanism of lactic acid formation used by the contracting muscle, and that the mechanism of lactic acid formation used by the muscle is radically different from that which has been described in cell-free extracts.

The author is indebted to the Department of Physics of the University of Michigan for the supply of radio-phosphorus used in these experiments.

69. Studies on Permeability of Tissue Cells to Phosphorus. AUSTIN M. BRUES, ELIZABETH B. JACKSON AND WALDO E. COHN, *Collis P. Huntington Memorial Hospital of Harvard University, Boston, Massachusetts.*

A technique has been developed whereby the uptake of radioactive substances by cultures of cells can be measured. The cells are grown on a coverslip 0.15 mm in thickness attached to one side of a roller bottle. By placing the bottle in a suitable position, the radioactivity in the cells, independently of that in the perfusing medium, can be measured without removing them from their environment.

With this method, it is possible to measure the permeability to and concentration of substances in isolated groups of cells. The effects on permeability of altering the constituents of the medium and other environmental factors can thus be demonstrated. In the course of experiments, parallel observations are made on the morphology and behavior of the cells by direct high-power microscope observations, and on chemical changes in the media brought about by cell metabolism.

We have studied by this technique some of the conditions attending the uptake of inorganic and some organic radio-phosphate compounds. Certain embryonic and adult tissue cells and tumor cells accumulate radio-phosphorus to a higher concentration than that in the extracellular medium. Growing cells take it up in significantly higher amounts than those which are surviving but not growing. The rate of uptake is most rapid in the first few hours. Cultures allowed to remain in the same medium until cell death occurs then release radio-phosphorus into the surrounding fluid. In this way, the behavior of cells towards radio-phosphorus can be used as an indicator of their viability.

Various effects of altering the constituents of the media, of growth inhibitors, and of specific enzyme poisons, on transfer of phosphate are being studied.

Biology IV

Biochemical Studies with Stable and Radioactive Isotopes

Chairman: DR. S. L. WARREN, *University of Rochester Medical School*

73. Nonphotochemical Reduction of CO_2 by Biological Systems. S. RUBEN AND M. D. KAMEN, *Department of Chemistry and Radiation Laboratory, University of California, Berkeley, California.*

Experiments with short-lived carbon (C^{11}) have shown a number of heterotrophic systems assimilate small amounts of CO_2[1-4] lending support to the view that CO_2 reduction is not exclusive to photosynthetic and chemosynthetic autotrophic organisms.[5] It seems reasonable to suppose the formation of reduced radio-carbon from labeled CO_2 is not due to simple interchange but rather that CO_2 is used as a specific oxidizing agent in one or

more steps in the respiratory mechanism. To elicit further information concerning the manner in which the CO_2 is utilized, an investigation of the metabolism of varied types of organisms using labeled carbon as a tracer has been inaugurated.

In addition to the heterotrophic organisms in which a net absorption or net evolution of CO_2 occurs during respiration (yeast, rat-liver, *B. coli*, ground plant roots, *P. pentosaceum*, *clostridium Acidi-Urici*), some autotrophic organisms which show a net absorption of CO_2 have been studied (*M. omelianski* and *Methanosarcina methanica*). A dark pick-up of CO_2 has also been observed with photosynthetic organisms.[6]

In studies with yeast[1] attempts to identify chemically the radioactive molecules resulted negatively. Most of the active carbon was extractable with boiling dilute acid. No acitivity was found in pyruvate. While the active material could be precipitated with Ba^{++}, very little could be decarboxylated. The chemical nature of the active molecules in yeast is apparently quite different from that observed in the dark pick-up by a photosynthetic organism such as *Chlorella*. The reversibility of the yeast CO_2 assimilation is being investigated.

The methane bacteria[2] have been found to reduce CO_2 to CH_4 as a result of the fermentation of methanol. An appreciable portion ($\sim$10 percent) of the radioactivity appeared in nonvolatile cell material. The propionic acid bacteria[3] which utilize CO_2 during fermentation of glycerol transformed 80 percent of the labeled carbon assimilated to propionic and succinic acids, the propionic acid being three times as active as the succinic. The remainder ($\sim$20 percent) of the C^*O_2 was incorporated in cell material. Glycerol enormously increased the CO_2 uptake as well as the ratio of C^* in the two acids. A mechanism based on these experiments will be discussed. The uric acid bacteria[4] ferment uric acid, xanthine and hypoxanthine to acetic acid, ammonia and CO_2 anaerobically. Evidence was obtained for the production of active acetic acid. C^* was found in both the methyl and carboxyl groups. The active volatile acid produced from uric acid appeared to be almost entirely acetic acid. The hypothesis of CO_2 as an oxidizing agent in fermentation seems to be borne out in these experiments.

The researches with C^*O_2 are being continued, and it is expected much useful information bearing on the mechanism of CO_2 reduction will be obtained.

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74. Biological Studies with Radioactive Carbon. A. Baird Hastings and G. B. Kistiakowsky, *Harvard University, Cambridge, Massachusetts.*

The fate of carbon compounds in the body has long engaged the attention of biochemists. Prominent in these numerous studies have been the attempts to elucidate the steps involved in the metabolism of carbohydrate. Although many steps concerned in the breakdown of carbohydrate are now quite well understood, the steps involved in the synthesis of glycogen from simple 3-carbon compounds are still obscure.

It has been demonstrated (confirming the work of Cori and Cori) that within 2 to 3 hours after feeding sodium lactate to a starved rat, there is a marked increase of liver glycogen, corresponding in amount to about 30 percent of the administered lactate. However, the exact origin of the carbon of the newly formed glycogen cannot be established by chemical means. The possible sources of the glycogen carbon include: (a) the 3 carbons of the original lactate molecule; (b) the 2-carbon residue left after decarboxylation and oxidation of the lactate molecule; (c) other glycogen precursors already present or formed in the organism; (d) carbon dioxide produced by metabolic activity.

With radioactive carbon (C″), experiments have been performed in an effort to determine from which of the above carbon source, or sources, the liver glycogen originates.

Lactic acid containing radioactive carbon in the carboxyl position was prepared by Dr. R. D. Cramer by a rapid synthesis requiring only 1½ to 2 hours (see paper by Dr. A. K. Solomon). This lactic acid, in the form of sodium lactate, was administered orally to rats; and, after a lapse of 2½ hours, the liver glycogen was isolated. The expired CO_2 was collected over the 2½-hour period and was found to contain about 15 percent of the radioactive carbon administered. The biochemical procedures were carried out by Dr. F. W. Klemperer and Dr. B. Vennesland. The radioactivity of the glycogen represented only a small fraction (1.6 percent) of the radioactivity administered, whereas the amount of glycogen formed corresponded to 30 percent of the lactate administered. This result precludes the possibility that the carbon of the glycogen originated directly and solely from the 3 carbons of the administered lactate molecules. It is also highly probable that the glycogen was not derived from any single category of the four carbon sources enumerated above, but rather had its origin in more than one source.

75. The Use of Organic Compounds Containing Stable Isotopes for the Study of Intermediary Metabolism. R. Schoenheimer, *College of Physicians and Surgeons, Columbia University, New York, New York.*

Work on the biological fate of organic compounds containing C, H, O and N is restricted to the use of stable isotopes, as with the exception of C^{14}, no radioactive isotopes with a sufficiently long lifetime is available for such experimentation at present.

The experiments are generally carried out in 4 steps:

(1) The compound to be investigated is prepared in the laboratory in such a way that one or more (stably bound) atoms are present in the form of the heavy isotopes. The synthetic methods employed are presented in another paper.

(2) A small amount of the compound is added for short periods to the ordinary diet of normal animals. The value of the compounds has restricted the work to small animals such as mice or rats.

(3) A number of pure compounds are isolated from the excreta and, after killing the animals, from their tissues.

(4) The isotope concentration of the isolated samples is determined, N^{15} by mass spectrometry and *D* by density or mass spectrometry. The methods will not be discussed.

If after administration of an isotopic compound *A*, an isolated compound *B* contains the isotopic tracer, this is an indication that *A* was either converted into *B* or *A* has been in chemical interaction with *B*.

The isotopes have furnished, for the first time, a tool for the investigation of occurrence and rate of chemical reactions going on among the tissue constituents of normal adult animals, i.e., of living organisms that keep constant the total amount and composition of their components. Almost all compounds investigated so far, even the large molecules, fats and proteins, were found to be involved in rapid and complex chemical reactions.

By adding small amounts of various isotopic (*D*) physiological fatty acids to the normal diet of animals it was found, that there occurs a continuous interconversion of one type of physiological fatty acids into others. Some are dehydrogenated while unsaturated ones are hydrogenated; the chain of some acids is shortened by 2 or 4 carbon atoms and the chain of others is elongated by the same number of carbon atoms. Aliphatic alcohols (cetyl alcohol) seem to be intermediates in these automatic reactions. In addition to the interconversion, there was observed a continuous synthesis from small molecular units simultaneous with a destruction of an equivalent amount of others. The newly formed fatty acids are introduced into fats; ester linkages open and close continuously. All these rapid reactions are so balanced that they do not lead to ultimate changes of total amount or composition of the animal fats. The highly unsaturated fatty acids, linoleic and linolenic acids, known to be indispensable food constituents, are exceptions; they are not involved in these processes.

Even more complex automatic reactions were found to occur among the amino acids of the proteins of living animals. The addition of small amounts of isotopic amino acids (N^{15}) to the normal diet, results in the presence of various isotopic amino acids in protein linkage. The result reveals the occurrence of continuous opening and closing of peptide linkages, deamination at alpha-position of temporarily liberated amino acids and simultaneous amination of nitrogen free substances, and the replacement of the amidine group in the arginine of the proteins by nitrogen from amino acids. Besides this continuous transfer of nitrogen among the constituent of proteins, the carbon chain of some amino acids is converted into that of others: ornithine is continuously converted into arginine, into proline, and into glutamic acid and phenyl-alanine into tyrosine. The amino acids newly formed by the various reactions replace the same type of amino acids in the proteins. Almost all proteins of the animal are involved in these extensive rearrangements; even the specific antibody of the serum of immunized animals. Only few compounds e.g. the amino acid lysine, do not take part in these processes. All these rapid reactions like those observed with fatty acids are so balanced that the total amount and structure of proteins is ultimately unchanged.

The nitrogen excreted by the animals is not that of the food, but a sample of the mixture originating from the extensive chemical interaction of the dietary amino acid nitrogen with the relatively large amounts of reactive nitrogen in the organ proteins.

The application of N^{15} and deuterium to normal animals in different laboratories has established the source of all parts of the creatine molecule. The glycine part is derived from glycine of the proteins and the amidine group is transferred from arginine of the proteins. Du Vigneaud and collaborators have synthesized methionine with an isotopic (deuterium) methyl group. Its administration resulted in the presence of isotopic creatine and isotopic choline. The methyl groups of both compounds are thus derived from methionine.

The experiments with the isotopic fats and proteins seem to show that all chemical reactions that the animal can perform are carried out continuously at a rapid rate. The opening of peptide, ester, and other linkages of the large molecules liberates active groupings which take part in metabolic cycles. Additional evidence for this theory is the finding that isotopic ammonia given to birds results not only in the formation of isotopic uric acid, which is excreted, but also of isotopic purines (adenine and guanine) which are introduced into nucleo-proteins. The purines of the nucleo-proteins thus seem to be involved in the process of uric acid formation.

Biology V

The Study of Animal Metabolism and Radioactive Tracers

Chairman: Dr. D. W. Bronk, *Cornell University Medical School*

82. The Use of Radioactive Sulfur, S^{35}, for Metabolic Studies. Harold Tarver and Carl L. A. Schmidt. *Division of Biochemistry, University of California Medical School, Berkeley, California.*

Next to nitrogen, the element sulfur is most commonly used as an index to protein metabolism. This is due to the fact that most proteins contain one or more of the sulfur-containing amino acids: cystine, methionine, and djenkolic acid. Many biologically important compounds contain sulfur. The fate of these compounds in the animal body is often determined by following the transformation and the form in which the sulfur appears in the excretory products.

Radioactive sulfur, S^{35}, with a half-life of 90 days, is particularly well adapted for studies dealing with sulfur metabolism. Thus, when methionine containing this isotope was fed to rats it was possible to isolate cystine containing S^{35} from the hair and tissues of the experimental animals, indicating the transformation of methionine to cystine. While the mechanism of this reaction is still not wholly clear, a tentative hypothesis is advanced to account for the facts.

Experiments of the above type often necessitate a new technique for the synthesis of a particular sulfur-containing compound. A simplified technique for the synthesis of methionine is presented.

The rate of the appearance of S^{35} in the proteins of egg white was determined by feeding methionine containing radioactive sulfur to hens. S^{35} was first found in the egg white on the second day and reached its maximum value on the fourth day.

Preliminary experiments on the appearance of radioactive sulfur in *p*-bromophenylmercapturic acid, when bromobenzene and S^{35} containing methionine were fed, are also reported.

The experiments cited above serve to indicate that radioactive sulfur is a particularly useful tool in studies dealing with the fate of sulfur-containing compounds in the animal body. It will probably be especially useful in the determination of rates of certain reactions that occur in living matter.

83. The Fate of Inorganic Arsenic in Certain Animals and in Man. F. T. HUNTER, *Massachusetts General Hospital*, AND A. F. KIP, *Massachusetts Institute of Technology, Cambridge, Massachusetts.*

Subcutaneous injections of radioactive potassium arsenite were given to 37 albino rats, 2 guinea pigs and 2 rabbits. The daily dose per kilo of body weight in all animals was about the same order of magnitude (minimum 0.3; maximum 1.6 mg). After a series of daily injections, usually four in number, the animals were killed at varying time intervals. During life, daily blood arsenic determinations were done and after death the arsenic content of the liver, kidneys, spleen, and in a few instances the brain, were made.

Rats.—The highest concentration of arsenic was found in the blood, the measurable amount being confined to the red corpuscles. It appeared to be attached to the hemoglobin molecule and on fractionation the globin portion yielded twice as much as the heme fraction. No arsenic was found in association with the stroma of the cell. In all cases the maximal concentration in the blood occurred 24 to 48 hours after the last injection, and at this time the total arsenic in the blood accounted for 50 percent to 60 percent of the total amount injected. The spleen showed the highest, the kidney the lowest concentration. Regardless of the daily dose, the concentration in these organs was maximal 24 to 48 hours after the last injection. Two animals previously given considerable amounts of ordinary arsenic showed somewhat higher blood levels of radioarsenic than controls. Splenectomy performed prior to injection did not appreciably alter the distribution of the metal.

Because our animals were all infected with *bartonella muris* and since this organism is localized within the red cell and is affected by certain arsenicals, some of the experiments were repeated on bartonella-free animals. This group of animals showed somewhat higher concentrations of arsenic in the liver and somewhat lower concentrations in the spleen, but the kidney concentrations were a great deal higher than in infected animals. The amount of arsenic excreted daily by these animals, as measured on mixed samples of urine and stool, showed a constant relationship to the blood concentration while arsenic was being given, but when arsenic was stopped, the excretion dropped rapidly to zero.

Guinea pigs and rabbits.—Two specimens of each type were studied. In all animals the blood arsenic was negligible. In contrast to rats, the liver arsenic of the guinea pigs was considerably greater than that of the spleen. The figures on the organs of rabbits have little significance since the livers of both animals showed heavy infestation with coccidia.

Studies on humans

Normal humans.—Two normal humans received 1.5 mg per day for four days. No arsenic could be demonstrated in the blood. Of the daily excretion via kidney and intestinal tract, 99 percent was excreted in the urine and only 1 percent in the stools. In both cases, 24 hours after the first dose, 50 percent of the amount injected had been excreted. This percentage excretion of the accumulated dose remained approximately constant until 24 hours after the last injection, when excretion dropped precipitously to less than 2 percent.

Leukemic humans.—One case of untreated chronic myeloid leukemia and one case of untreated lymphoblastic leukemia were studied. No arsenic could be measured in the blood. Excretion took place almost entirely via the kidneys, but 24 hours after the first injection, only 20 percent of the injected dose was recovered in the urine. As the experiment continued, the percentage excreted of the accumulated dose rose gradually to about 40 percent. Twenty-four hours after the last injection, the excretion via the kidneys began to fall and fell gradually, over three days, to about 2 percent of the total injected. The case of lymphoblastic leukemia came to autopsy and complete determinations of the arsenic content of all the organs were made.

84. Metabolism of Arsenic Compounds. OCTAVIA DU PONT, IRVING ARIEL AND STAFFORD L. WARREN, *Strong Memorial Hospital, The University of Rochester, Rochester, New York.*

Small volumes of solutions containing small subtoxic amounts of radioactive arsenic in the form of pentavalent arsenate were injected into the rabbits' ear vein and the animals sacrificed at various intervals from 5 minutes to 168 hours after injection. Radioactive arsenic content was

determined on from 15 to 25 different organs in each of the 25 rabbits by the usual Bale technique.

The expected widespread distribution and prompt excretion in the urine occurred quickly. After the first hour the blood concentration slowly fell to almost disappear by the 168th hour. The concentration in the liver, lung, muscle, bone, and tumor rose to a peak rather quickly by the third hour and fell by the 12th hour. Almost 50 percent of the total injected may be excreted in the urine by the 12th hour. For the liver and kidney where the concentration rises to the highest levels per gram of tissue, the critical period from the single dose apparently begins at the third hour, and is much less hazardous by the 12th hour. Storage in muscle, bone, tumor, and lung also seems to parallel the changes in concentration although at a lower level. There is a considerable amount of variation from animal to animal but the relative values are comparable. Concentrations in various glands and other organs are low and in some cases (brain) surprisingly so. The high values in the tumor are apparently not directly related to its blood content.

This work is the basis for further studies with complex arsenical compounds.

85. The Course of Vitamin B_1 (Thiamin) Metabolism in Man as Indicated by the Use of Radioactive Sulfur. HENRY BORSOOK, JOHN B. HATCHER AND DON M. YOST, *Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California.*

Experimental methods.—For the quantitative measurement of the low activity of samples of radio-sulfur, which emits beta-particles with the low energy of (0.107 Mev), the coincidence method was used. The two sulfide-coated copper Geiger counter tubes were enclosed in a large, partially evacuated bell jar and the samples were carried to position in front of the slots in the counter tubes by an externally operated chain belt arrangement. The amplifiers, utilizing the standard Rossi coincidence circuit, had time constants of 3×10^{-4} second and single counts of the two counter tubes as well as the coincidence counts were scaled by thyratron type scales-of-eight and recorded on Cenco recorders. Many of the weaker samples were measured over a period of days, the background and sample measurement being alternated for short periods. The activity of the sample and the satistical error of the measurement were calculated from the total number of counts; a run was discarded unless the short period counts of sample or background agreed to within their probable errors.

The sulfur from the original material was precipitated as barium sulfate, converted successively to barium sulfide, hydrogen sulfide, and finally to elementary sulfur. The final samples for measurement being made from the elementary sulfur made into films of known area and "infinitely thick" to the weak radiation (greater than 15 mg/sq. cm). Depending upon the sample the over-all absolute errors of measurement of quantity of radio-sulfur varied from 1.2 to 30 percent.

Results.—Thiamin synthesized from radio-sulfur was injected intramuscularly in two series of experiments, using a human subject on a normal and on B_1-free diet. Determinations of the free (unphosphorlyated) B_1 in the urine were made by the thiochrome method, and the radioactive sulfur of the feces and of the inorganic sulfur, ethereal sulfur, and neutral sulfur compounds in the urine were determined.

Rapid destruction of the injected thiamin was indicated in both experiments by the appearance of the radio-sulfur in the inorganic fraction of the urine, in amounts increasing to about 15 percent of that injected daily. No radio-sulfur was found in the ethereal fraction.

In the neutral sulfur fraction of the urine the excreted radio-sulfur during the period of injections was less than that corresponding to the free B_1 found, indicating the rapid interaction of the injected material with that already present in the tissues, and the displacement of pre-existing thiamin. After 36 days of the B_1-free diet the injection of 8 mg of radio-B_1 over a period of three days resulted in the excretion of 0.8 mg of pre-existing thiamin. On discontinuing the injections the destruction of B_1 was again indicated by the appearance of quantities of radio-sulfur greater than that corresponding to the free B_1.

On the normal diet a total of 61 percent of the injected thiamin was recovered from the urine and 11 percent from the feces over the period of the experiments. Of the urinary radio-sulfur recovered, 25 percent represented destroyed thiamin appearing as inorganic sulfate and 18 percent destroyed thiamin appearing with the neutral sulfur compounds.

86. The Use of Radioactive Elements in Insect Physiology. RODERICK CRAIG, *Division of Entomology and Parasitology, University of California, Berkeley, California.*

In the study of insect physiology we are not only interested in normal physiology but even more in derangements of the normal produced by toxic materials, since man's chief interest in the insect where toxins are used is to destroy it. Our fear of insects is more than justified when one considers that insects are responsible for malaria, which causes more loss than any other disease, and several other important human and animal diseases. No less important is the agricultural damage caused not only by the feeding of insects but by their transmission of plant virus diseases. A knowledge of insect physiology is essential in understanding the role of the insect as a vector of animal and plant disease and equally essential in understanding the mode of action of poisons used to kill the insect. The insect is so small that in most cases the presence of a toxic material cannot be determined by ordinary analytical methods. Since public health hazards have necessitated the limitation of insecticide residues on foods, new insecticides have been sought, many of them organic compounds. The increasing importance of organic insecticides will require more study of toxicologic action which can often be carried out by use of tracer elements.

Many problems in insect physiology are unsolved today because no adequate technique has existed. Such general problems as absorption, excretion, distribution of substances

and intermediary metabolism have had to await analytical procedures delicate enough to determine fractions of a microgram of material.

The technique used with tracer elements is the same as that in larger animals. The radioactive element is either fed or injected parenterally. If the distribution of the material is the principal object, the insect is sectioned with a freezing microtome and radio-autographs obtained. If quantitative studies are desired, the portions of the insect are ashed and the activity determined in the usual way with either an electroscope or Geiger counter.

In 1935 M. A. Hamilton[1] used polonium to show the amount of material removed from a plant by a feeding aphid and also the amount of the ingested material returned to the plant during the next feeding period which was of the order of 0.1 mm³. This sort of work might be extended with profit to a study of insect vectors of human disease. Patton[2] in 1939 used radioactive sodium to show the path of excreted material in the yellow meal worm. In this case the volume of fluid being studied is about 1 mm³.

At the present time the role of phosphorus in metabolism, the rate of circulation of the insect blood and the rate of absorption of simple substances are being studied. Since we know that phosphorus is present in the blood of insects in amounts of 5 to 20 times that found in mammals and since during the developmental period of most insects large quantities of fat are stored, one would expect the role of phosphorus to be very important and easily studied. Preliminary studies by means of radio-autographs of the tissue of insects fed on radioactive phosphorus as phosphate have shown that the phosphorus is largely concentrated in the actively metabolizing cells. The rate of circulation of the blood cannot be directly studied because of the open circulatory system, but the time required to give a uniform distribution of a substance in the blood can be estimated. Much work will be required to determine the normal limits and factors affecting rates of distribution. The absorption of phosphorus and sodium from several regions of the alimentary tract of insects is being studied by the same technique as used by Patton in his work on excretion.

[1] M. A. Hamilton, Ann. App. Biol. **22**, 243–258 (1935).
[2] Patton, J. Exp. Zoöl. **81**, 437–457 (1939).

Biology VI

Studies of Plant Metabolism with Radioactive Isotopes

Chairman: DR. D. R. GODDARD, *University of Rochester, Rochester, New York*

87. Studies in Photosynthesis with Radio-Carbon. M. D. KAMEN AND S. RUBEN, *Radiation Laboratory and Department of Chemistry, University of California, Berkeley, California.*

The short-lived radioactive carbon, C^{11} (half-life = 21 minutes), has been used to study the reduction of C^*O_2 by green plants.[1–5] The bulk of the work has been carried out with the unicellular green alga, *Chlorella*.

Chlorella, as well as higher plants (sunflower and barley) assimilates[2] small quantities of CO_2 in the dark. The dark pick-up exhibits the same sensitivity to various inhibitors (HCN, phenyl-urethane, ultraviolet light) as does normal photosynthesis and is not associated with the respiratory processes. It is reversible and independent of chlorophyll concentration.

Simultaneous measurements on the rate of CO_2 reduction in the light by manometric methods and the radioactive technique give identical results within the experimental error. Hence, exchange reactions can account for very little of the CO_2 reduced in the light.

Chemical tests on the water soluble material formed in the light and dark indicate the presence of at least one alcoholic hydroxyl and one radioactive carboxyl group in the active molecules. Attempts to identify the active compound as one of a large number of organic substances known to exist in plants (i.e., sugars, aldehydes, ketones, proteins, etc.) were unsuccessful. In particular, the presence of such intermediates as formaldehyde or low molecular weight organic acids seems to be excluded.

The major part, if not all, of the C^*O_2 taken up in the dark was found in carboxyl. A smaller but appreciable fraction of the light reduction products was in $-COOH$ groups. From measurements of the diffusion constant and sedimentation velocity, the molecular weight of both light and dark reduction products is in the close neighborhood of 1000.

While no radioactive reducing sugars are formed in *Chlorella* even after 100 minutes of exposure to C^*O_2, about 20 percent of the water soluble activity from the higher plants can be recovered in this form after exposures of an hour.

The experiments performed with radioactive carbon suggest a tentative mechanism for photosynthesis in which the first step in CO_2 reduction is a reversible nonphotochemical process with the formation of carboxyl, *viz.*:

$$R\,H + CO_2 \rightleftarrows R\,COOH$$

Here, R is a large molecule—in all probability a part of an aggregate of very high molecular weight. Several analogous reactions are known in organic chemistry. The light reaction can be written:

$$R\,COOH + H_2C \xrightarrow{h\nu} R\,CH_2OH + O_2.$$

The energetics and advantages of this approach will be discussed.

[1] Ruben, Hassid and Kamen, J. Am. Chem. Soc. **61**, 661 (1939).
[2] Ruben, Kamen, Hassid and DeVault, Science **90**, 570 (1939).
[3] Ruben, Kamen, Hassid, J. Am. Chem. Soc., in press.
[4] Ruben, Kamen, Perry, J. Am. Chem. Soc., in press.
[5] Ruben and Kamen, J. Am. Chem. Soc., in press.

88. Use of Irradiated Elements as Tracers in Investigations of Mineral Movement in Plants. F. G. GUSTAFSON, *Department of Botany, University of Michigan, Ann Arbor, Michigan.*

For many years plant physiologists have been investigating the path of the upward movement of minerals in plants. In most of these experiments the different tissues have been analyzed for the particular mineral under investigation, and this is not easily done.

With the preparation of artificial radioactive chemicals by means of the cyclotron, a new method of approach to this problem was made available. The irradiated elements could be used as tracers, and, as small quantities can be detected, short intervals of exposure to the chemicals could be used. As far as is known to the writer, only three groups of investigators have thus far made use of this method in this country: Gustafson and Darken at Michigan, Bennett and Stout and Hoagland at California. The elements potassium, phosphorus, sodium and bromine have been used in these experiments. The first two are found abundantly in plants and are, therefore, well suited for such experiments.

The procedure has been to use intact plants rooted either in solution or sand medium. The roots have been uninjured. Gustafson and Darken applied the irradiated phosphorus as a 0.5 percent solution of KH_2PO_4, while Stout and Hoagland have incorporated their active material in carefully balanced nutrient solutions. The activity in the plant has been determined either by an electroscope or a Geiger counter. The length of the exposure to the radioactive material has varied from a few hours to three days.

The set-up has varied a little with the different investigators. All investigators have used experiments in which a section of the bark was separated in the middle from the wood and the amount of active material present in different sections of wood and bark determined. Gustafson and Darken also set up experiments in which a ring of bark was removed from one plant and a section of wood of the same length from another plant, and the amount of active phosphorus above the cut compared with a third plant intact, or they removed all of the wood leaving a strip of bark to which were attached several leaves, and determined the amount of irradiated phosphorus in the bark or/and leaves.

In an experiment with Bryophyllum lasting 40 hours, Gustafson and Darken found that phosphorus was present in the bark which had leaves attached to it but was itself attached to wood only at the base. They found active phosphorus as far as 23 cm above attachment, and, in experiments where leaves were tested, they also contained active material. In other experiments where wood or bark was removed there seemed to be no appreciable difference in the amount of activity found some distance up the stem either in the wood or the bark. In other experiments where a section of bark was loosened from the wood they found that there was active phosphorus in all parts of the bark, which was attached to wood only at the ends. From these and other experiments they came to the conclusion that minerals are conducted upwards in the bark as well as in the wood.

With a set-up similar to the last mentioned, Stout and Hoagland used cotton, willow and geranium plants. The time the plants were in solution was shortened to only a few hours, but with bright sun and wind movement the transpiration was quite active. Their published report shows that the middle sections of the bark, which was separated from the wood, had the least activity and that the two ends, which were in contact with the wood, had the most. Therefore, their interpretation is that the activity in the middle sections was partly due to downward diffusion.

From their experiments they came to the conclusion that minerals move upward only in the wood of a stem. They explain away the difference between their findings and those of Gustafson and Darken as being due to difference in the length of the experiment. In experiments lasting for a longer time they maintain there is more of an equilibrium obtained and pure diffusion may play a much greater part, masking the relatively rapid movement of materials in the transpiration stream. In a more recent paper Gustafson shows that much less material is conducted into the upper part when the wood is cut than when the bark is cut, but he still believes that there may also be some upward conduction in the bark.

In these investigations the radiated elements have proven themselves of great value, because by their use tedious analyses have been avoided and much shorter periods of experimentation have been permitted.

89. Applications of Radioactive K, Rb, Na, P, and Br to Studies of the Mineral Nutrition of Higher Plants. P. R. STOUT, *Division of Plant Nutrition, University of California, Berkeley, California.*

Radioactive indicators have been used by a number of the staff members of the Division of Plant Nutrition at the University of California at Berkeley in studies pertaining to plant physiology, soils, and plant and soil interrelationships. Potassium and phosphorus are essential elements for the nutrition of higher plants. Sodium, although not recognized as essential, is often absorbed in large amounts from soils containing it, and frequently plays a predominate role in the physical condition of arid and semi-arid soils. Normally rubidium and bromine do not occur in plants or soils in amounts detectable by usual analytical methods. The latter however, when made available to plants, are readily absorbed without interfering seriously with their metabolism. Consequently, rubidium and bromine have been used as indicator ions in investigating the process of absorption, accumulation, and translocation of mineral nutrients by plants. Since radioactive isotopes have been made available to investigators at the University, it has been possible to run experiments using the elements physiologically required by plants. In addition to the obvious experimental advantages of tagged ions involved in normal physiology of plants, the extreme sensitivity with which the isotopes can be detected has permitted observations to be made of small sections in

relatively short periods of time. Various problems investigated will be reviewed and discussed under the several categories by which radioactive isotopes take their place as new and indispensable research tools for biological investigations namely (1) where the nature of the experiment requires an indicator ion of the element in question, and direct evidence can be obtained in no other way (2) where the number of plants required for an appropriate statistical treatment of "control" *versus* "treatment" would be so great as to be difficult if not impossible to achieve experimentally, and (3) where the sensitivity permits analyses of small amounts for which suitable chemical methods are not at present available. Of great interest to the investigator is an unexpected revelation that comes from new techniques. Removal of ions from the root environment to the tops of plants eight to ten feet high in 15 minutes, a very rapid lateral transfer of solutes from the wood to the bark, and the outgo of potassium from roots during the process of accumulation are cases in point. Slides of radio-autographs showing the distribution of phosphorus in various plant tissues will be shown.

90. Ion Movement in Living Protoplasm. S. C. Brooks, *University of California, Berkeley, California.*

The experimentally or naturally induced changes in the ion content of protoplasm are important in maintenance of its integrity within tolerable limits. Small changes in physical aspects are probably a factor in controlling the amount and direction of metabolism. Salt effects on metabolism are known. Without changing the total salt content to a cell it is possible to readjust the proportions of ions in cells to changing salt environments, i.e., to set up a statistical equilibrium between cells and environment for all ions. This implies ionic exchange. Using tracer ions it is possible to show that this equilibrium is approached enormously faster than suggested by traditional experiments. Work has been done with Na^+, K^+ and Rb^+, and Br^- and $HPO_4^=$ (all radioactive); an alga (*Nitella*), marine eggs, a fresh water amoeba and other forms were used. *Nitella* was studied most carefully. The proportion of protoplasm in representative samples was determined. The sap and protoplasm were separated and, utilizing the proportion found, determinations were made of the concentrations in each portion of the isotope in question after various intervals of immersion in dilute solutions of salts of radioactive isotopes. During the first few hours no salt reached the vacuole, but within 2–5 minutes the radioactive isotopes penetrated into the protoplasm in concentrations greatly exceeding the external concentration, e.g., 0.005*M* K*Cl. This ion cannot be only in the plasma membrane; the latter can combine with only about 1/100 or less of the observed amount of the ion. This amount is a considerable fraction of the total combining capacity of the total protoplasm for comparable ions. It is believed that the entering (tracer) ion displaces similar ions (e.g., Na^* for Na^+ and K^+) and also hydrogen or organic bases. The amounts of different ions in the protoplasm were found to differ so that Rb>K>Na. This can be predicted on the basis of colloid chemistry. This ion entrance, called induced accumulation, can be reversed by replacement of the isotope containing solution by salt solutions (Li, Na, K, Rb or Cs chlorides, 0.01*M*) but only very slowly by distilled water. Hence, ion exchange is necessary for the movement of ions in this process.

Following induced accumulation there appears to be loss of the isotope followed by alternating further intake and loss phases. Losses appear to involve loss of total salt content, i.e., simultaneous exit of cation and anion. Changes in ion content would themselves alter the protoplasm, possibly accounting for permeability changes and hence losses. The later intake may lead to ion contents still higher than the previously noted maxima. Both loss and intake depend at least partly on metabilism, as shown by the disappearance or reduction of these changes in cells killed by heat or narcotics. Cyanide is ineffective.

Compatible results were obtained with other algae and *Amoeba proteus*. Marine eggs show relatively slow ion exchange, thus agreeing with findings of other workers on erythrocytes, muscle, etc. A possible correlation is suggested of high permeability with a normal salt-poor environment. In *Nitella*, protoplasm alkali metal ions move with rates comparable with water and small non-electrolyte molecules (10^{-7}·G·cm^{-2}·hr^{-1}) rather than the traditional rates of $10^{-9}-10^{-8}$ established by determinations of total salt content or made on vacuolar sap.

Radiology I

General Aspects of Cancer Therapy

Chairman: Dr. G. W. Holmes, *Massachusetts General Hospital*

24. Pathological Analysis of the Action of X-Rays and Radium on Tumors. Fred W. Stewart, Pathologist, *Memorial Hospital, New York, New York.*

It is impossible to summarize the subject matter of this discussion in a few words. The complexity of the field of human tumors and the different morphologic mechanisms involved in their behavior toward x-rays and radium permit no satisfactory generalizations. The subject is still in the stage of descriptive analysis, best discussed in terms of examples of behavior of various individual tumors as they occur in different individuals.

An effort is made to discuss the subject under four

topics:—(1) Evidences for direct action of physical agents on the tumor cell or portion thereof; (2) effects on the connective and supporting tissues and their influences on the behavior of the tumors; (3) alterations produced in the circulatory pattern and their effect on the cancer; (4) undefined differences in individuals which seem to alter the relations between tumor and host.

Various morphologic changes in tumors are individuaized and attempts made to discuss them in terms of physical theory and to estimate their importance in the regression of individual tumors. The insufficiency of current physical theory in accounting for the various processes seen to have occurred in radiated human cancers is emphasized. By insufficiency in theory is not meant necessarily that theory offers an erroneous concept of how radiation affects tumor cells,—not a denial of the fundamental ionizing effect of x-rays and radium in cells and their surrounding media—but a lack of knowledge as to why different lesions do or do not show morphologic changes compatible with theory.

The morphologic factors involved in radiosensitivity are emphasized as complex phenomena requiring individual analysis, and determination of the probable radiosensitivity of a tumor is believed to be only possible from observations on group behavior, individual lesions occasionally varying widely in their response.

25. Chronological Factors in Radiation Therapy. HENRI COUTARD, *Chicago Tumor Institute, Chicago, Illinois.*

The chronological factors may be defined as the time which separates the beginning of the treatment and the moment of its effect upon the cells. Treatment thus dissociates and characterizes the cellular types so well that the differences of radiosensitivity between two groups of cells become measurable by their chronological factors. This chronological factor may also constitute a physiologic relationship between the conditions of a treatment of minimum intensity and maximum effects.

When the chronological factor is of short duration, one to six days, the action on the cells has been considered as one of direct and individual destruction, because all irradiation, even slight, awakens or accelerates the cellular processes of multiplication, all the more strongly as the cells are less differentiated. Cellular fragility is thus increased and destruction is facilitated.

When the chronological factor is of longer duration, more than 13 days, the action of the rays cannot be considered as a direct and individual one. An intermediate factor intervenes, which is the underlying soil or tumor bed. Under the influence of daily irradiation, when they are reaching a certain threshold, there is produced through the intermediary of the irradiated substrata, a grouping and concentration of the moments of cellular multiplication. The moments of cellular disappearance which sooner or later follow them become simultaneous and of short duration. They are, for example, of 2 or 3 days duration for the mucosal and skin, which have their moments of disappearance from the 13th to the 15th day for the mucosal, from the 26th to the 28th day for the skin, after an intense series of irradiation given from the 1st to the 7th day.

The collective chronological factors, under the influence of substrata, are substituted for the individual chronological factors. An indirect effect is substituted for one which was considered as a direct effect.

If, instead of a treatment of 12 days, one irradiates the mucosal and the skin throughout 40 days, with small daily doses, the moments of grouping of concentration and of disappearance are of longer duration—5 to 6 days. They are incomplete, a small number of cells participate in this disappearance. But this is repeated at varying intervals. One thus causes chronological factors to appear which always have a collective tendency but also a periodic character. Cellular disappearance attains its greatest height at fixed moments, which are precise and repeated on the 13th, 26th, 39th and 52nd days for the mucosal, and on the 26th and 52nd days for the skin.

This method of continuous and prolonged irradiation when using higher daily doses has demonstrated its efficacy on cancers moderately differentiated. If we compare continuous treatments, which were terminated, respectively, on the 12th, 26th and 39th days, we see that they have given us a proportion of five-year survivors three times greater than when they have terminated between the moments of the periods, on the 19th, 33rd and 46th days, and using doses comparatively equal. The total dose can thus be reduced when the treatment ends at the moment of a period. At this moment cellular fragility reaches a maximum. Larger doses, on the contrary, are inefficacious, if the treatment ends between the moments of the periods. The effects produced under these latter conditions are antiphysiologic, accompanied by local and general disturbances. There is an opposition to the concentration of the time of multiplication.

To obtain satisfactory results in more differentiated cancers, it is necessary to increase the daily dose, all the more so as the differentiation is more marked. Continuous treatments do not permit, without grave danger, sufficient daily dose to allow the substrata to group and closely concentrate. Thus we must use treatments which are not continuous, of short duration, but intense, in series, utilizing the times and moments so that the effects are produced at the moments of the periods, when the cellular fragility is maximum. For certain cancers it has been sufficient to cause the time of irradiation to coincide with the periods, which simplifies the problem.

The most simple and effective treatments have been those in which the number of series and the daily doses were increased parallel with the degrees of differentiation, as in the three following examples: (1) Cancer slightly differentiated—two series of 6 days separated by 14 days without treatment. Daily doses 500 to 700 r. Doses of the series 3000 to 3500 r. Total doses 6000 to 7000 r. Duration 26 days. (2) Cancer moderately differentiated—three series of 3 days separated by 7 and 10 days without treatment. Daily doses 800 r. Doses of the series 2400 r. Total dose 7200 r. Duration 26 days. (3) Cancer very differentiated—four series of 2 days separated by 9, 11

and 11 days without treatment. Daily doses 800 to 1000 r. Doses of the series 1800 to 2000 r. Total dose 7600 to 8000 r. Duration 39 days.

Thus the chronological factor has become, in the case of skin and mucosal, and of cancers arising on these teguments, a factor both collective and periodic whose period corresponds to that of the larger physiologic phenomena having to do with cellular multiplication. The cutaneous period which reappears every 26 to 28 days corresponds to the ovarian period. Its duration of 2 to 3 days corresponds to the duration of the elimination of utero-vaginal epithelium. The chronologic factor of the mucosal corresponds to the half-period of the ovary. It is remarkable that the phenomena of cellular elimination, which appear monthly under the influence of physiologic factors, can appear artificially with the same period, under the influence of irradiation. If these are due in the first case to the products of complex hormonal glandular secretions, it is possible that they are due, in the second case, to physiologic factors, little different from the preceding, but localized and activated by the action of the rays on the substrata and surrounding tissues.

Radiology II

Radium and Roentgen Therapy

Chairman: DR. G. E. PFAHLER, *University of Pennsylvania*

37. The Present Status of Radium Therapy. DOUGLAS QUICK, *New York, New York.*

This discussion of radium therapy will be concerned chiefly with its place in the field of cancer plus a few closely allied or border-line conditions. Few of the malignant neoplastic diseases are manageable to best advantage by one agent or method alone. Radium has certain peculiar advantages to offer in the various combinations of therapy found best suited to the individual case, in the present state of our knowledge of the subject. Inasmuch as it does not afford the sole means of treatment in most of the major groups of malignant disease, it does not seem wise simply to enumerate its relative importance in the various groups ordinarily discussed by clinicians. The various special advantages will be suggested and their adaptation to certain fields of cancer presented.

In ordinary practice, there are three general methods of application, external or surface, intracavitary, and interstitial. The surface applications, usually in relatively small amounts, are used for skin lesions, while large amounts at substantial distance from the body surface, usually referred to as telecurietherapy, are used for depth doses in deep-seated tumors. In this one particular, its approach to a parallel or competitive position with x-ray therapy will be discussed. The peculiar adaptability of radium to intracavitary application approaches more nearly its real place in irradiation therapy. It affords a source of powerful energy in small bulk which can be placed in the body cavities for intense local irradiation. Probably the best example of this is in treatment of the uterine cervix and fundus. This principle of intense local irradiation at or near the center of the malignant neoplastic area is carried one step further in interstitial irradiation. Sources of radiant energy are implanted in and about the tumor bearing area. For this purpose radium salt in metal needles or radon in small celled metal containers (seeds) is employed. The relative values of each will be discussed and their wide range of application, especially in conjunction with operative surgery, will be pointed out.

It is rather generally accepted that the gamma-radiation is the all important factor. While this is probably true in large measure, the present trend of the day toward production, electrically, of shorter and shorter wave-lengths may be carrying us away from an important quality of radiation, even though its field of usefulness is limited. At least, the question of the value of beta-rays of radium will be raised. In its intimate application within tissues, radium has never, in a practical way, gotten beyond the interstitial implant. At one time it was visualized as a possible constitutional agent and certain clinical experimental work carried out. Ordinary table salt was exposed to radium emanation, dissolved in sterile water, and injected intravenously. A pronounced effect was noted in the leukemias, but the difficulties and hazards of the work caused it to be abandoned without publication of a report. It is now of interest in view of the radioactive substances made available through the agency of the cyclotron.

To date, the therapeutic advances with radium have depended largely upon adaptation of the various physical factors to the individual problem. Dosage, for the most part, has of necessity been the maximum that the normal tissue structure would tolerate. There has been no secondary or complementary agent, either biological or chemical, which would render the tumor tissue more sensitive to irradiation or aid in retaining more of the ionizing radiation within the tumor bearing area. The use of colloidal lead a few years ago was transiently regarded as a possible "sensitizing" agent, but failed to prove ultimately of value. Some of the more recent experimental work, particularly that reported by Failla of injecting sterile water into the tumor immediately following irradiation by x-rays, seems more encouraging. It is hoped that, by setting forth the shortcomings of radium, rather than its accomplishments, before a mixed group of scientists, effort may be stimulated toward solving some of the problems which would enable radium to embrace a wider field of usefulness.

The tremendous advances made during the last few years in the development of equipment for x-ray therapy

have rather overshadowed the older source of radiation—radium. Its adaptability in conjunction with x-ray therapy should be more carefully borne in mind by all clinicians, especially the roentgen therapists. It should also be noted that far too many physicians having a limited knowledge, or no knowledge, of the principles of radiation therapy, are coming to dabble in the use of radium. Such practice not only does irreparable harm to the patient but discredits both radium and x-ray therapy.

38. The Present Status of Roentgen Therapy. U. V. PORTMANN, *Cleveland Clinic, Cleveland, Ohio.*

The remarkable progress and extending usefulness of roentgen therapy for many inflammatory and malignant diseases have been the result of the collaboration of engineers, physicists, and biologists with the physicians.

Different types of apparatus have been developed to furnish irradiation in a wide range of quality and in adequate quantities. Means have been provided so that radiologists can administer treatment safely with considerable accuracy, and they can estimate the tissue reactions which will be produced. Consequently, the results of roentgen therapy are improving constantly.

However, roentgen therapy has limitations. Some of the clinical difficulties are inter-related and include those that are technical or attributable to the anatomical location and extent of the diseases being treated, and also to a lack of sufficient information about normal and pathological cellular functions. Clinical problems which may be solved by investigation in biophysics and biochemistry will be presented for consideration.

39. Supervoltage Roentgen Therapy. RICHARD DRESSER, *Collis P. Huntington Memorial Hospital of Harvard University, Boston, Massachusetts.*

A discussion of supervoltage roentgen therapy naturally resolves itself into a comparison between results obtained with wave-lengths produced in the neighborhood of 200 kilovolts and those obtained at higher potentials. Many radiologists have made the observation that the shorter wave-lengths are more effective in the treatment of certain types of malignant disease. Radium has been extensively used for superficial application, but it is available in such small amounts that the effective dosage at some distance below the surface cannot be obtained. Thanks to the efforts of physicists and engineers, x-radiation approximating in wave-length the gamma-rays of radium is now available in huge intensities. The output of one supervoltage x-ray machine is equal to several times the intensity which might be obtained from all the refined radium in the world. The physician may now avail himself of the penetrating qualities of these supervoltage roentgen rays and may place the source of radiation at a distance sufficiently great from the patient so that the effect of the inverse square law in the dosage delivered to deep-seated malignant neoplasms becomes negligible.

There are two important requirements of a therapeutic x-ray machine. First, it must be mechanically reliable so that a preconceived course of therapy can be carried out without interruption. Second, the output of radiation must vary within narrow limits. The period of mechanical instability of the electrostatic belt conveyor type of supervoltage apparatus developed at the Massachusetts Institute of Technology has been incredibly short. The original unit installed at the Huntington Hospital operates with the reliability of a commercial 200-kv machine. The apparatus is now being run routinely at 1000 kv, 1 milliampre, 70 cm distance, filtration 3½ mm of lead plus 8 mm copper. The radiation thus produced has a half-value layer of 10½ mm of copper or 4 mm of lead. The intensity is 70 roentgens per minute. This output could be nearly tripled if the machine were operated at its full amperage capacity. Since the unit is chiefly used in the treatment of deep seated malignancies, it is of interest to compare depth doses obtained at 1000 kv with those obtained at 200 kv. This comparison is shown in the Table I.

Million-volt radiation is found to possess several advantages: there is less scattering; the intensity below the surface (depth dose) is greater; the depth dose is largely independent of the size of the portal of entry. Moreover, clinical and animal experiments have shown that the tolerance of the skin to supervoltage x-rays is considerably increased.

The results obtained from the medical use of superhard radiation have been entirely in accord with what was anticipated from physical measurements. The response of a new growth to radiation is primarily dependent on three factors: first, the radiosensitivity of the growth; second, the total amount of radiation given; third, the rate at which radiation is delivered. A neoplasm which is not affected in any degree by 200-kv rays does not usually respond to the shorter wave-lengths. The lack of scattering, the greater penetration, and the employment of small portals of entry without appreciable effect on the depth dose result in better tolerance of supervoltage roentgen rays on the part of the patient. The total dosage can be increased, and the time of administration decreased. Two hundred-kilovolt treatment is usually limited in amount by the tolerance of the skin. At 1000 kv the factor of skin tolerance becomes

TABLE I.

PORTAL OF ENTRY		200 KV 70 CM ½ MM CU %	1000 KV 70 CM 3.5 MM PB 8 MM CU %
100 sq. cm			
	Surface back scatter	24	6.5
	Depth dose— 5 cm	67	77
	Depth dose—10 cm	34	49
	Depth dose—15 cm	17	29.5
	Depth dose—20 cm	8	18
225 sq. cm			
	Surface back scatter	26	9
	Depth dose— 5 cm	71	78
	Depth dose—10 cm	42	50.5
	Depth dose—15 cm	22	32.5
	Depth dose—20 cm	10.5	21
400 sq. cm			
	Surface back scatter	33	11
	Depth dose— 5 cm	77	79
	Death dose—10 cm	45.5	53
	Depth dose—15 cm	25	36
	Depth dose—20 cm	12.5	23.5

negligible and one is concerned with the reaction in the deeper structures. The combination of these factors has resulted in better regression of deep seated neoplasms than has hitherto been observed, and the results are improving as we gain greater knowledge of depth dose technique.

The one outstanding disadvantage of superhard radiation is in the treatment of superficially located tumors. The production of a sufficiently intense superficial reaction may result in damage to underlying vital structures. Even this could be technically overcome by shortening the distance from the source of radiation to the patient, but we have found it easier and perhaps as effective to use the longer wave-lengths in such instances.

I am indebted to Mr. Bernard Cosman and Dr. Milford Schulz for their collaboration in making depth dose measurements.

Radiology III

Neutron and Artificial Radioactivity Therapy

Chairman: DR. R. H. STEVENS, *Detroit, Michigan*

62. Neutron Beam Therapy. ROBERT S. STONE AND JOHN C. LARKIN, *Division of Roentgenology, University of California Medical School, San Francisco, California, and The William H. Crocker Radiation Laboratory, University of California, Berkeley, California.*

The production of fast neutrons in sufficient quantities for clinical use was first accomplished with the 37-inch cyclotron in 1938. In September of that year, treatments commenced on a series of 24 patients using neutrons produced from eight million-volt deuterons striking a beryllium target. Treatments were given once a week. Large total doses were given in a single sitting. It was found that approximately 200 *n* given to the face and neck produced a well-marked erythema, whereas doses as high as 270 *n* did not cause blistering. Doses as low as 70 *n* on the flexor surface of the forearm produced just visible reactions. Tumor regressions were obtained.

In November, 1939, the new 60-inch cyclotron producing 16 million-volt deuterons became available for clinical use three times a week. The average intensity of the beam of neutrons has been 5 *n* per minute. Up to September 10, 1940, 47 patients have been subjected to fractionated treatments. The patients were selected from that group of cases usually too advanced for treatment with x-rays, radium, or surgery. All the head and neck cases had metastatic involvement of the cervical lymph nodes. The lesions of the breast and prostate were inoperable, and some had distant metastases. The location of the lesions were as follows: breast (primary or recurrent) 6, prostate 5, stomach 1, head and neck 32, brain 1, and ovary 1.

The general plan of treatment was to use 50 *n* per field using 7×7 cm, 10×10 cm, and 10×15 cm ports in much the same manner as with x-rays. This was decreased when a patient showed too severe reaction or when the apparatus was not running at a maximum efficiency. The total doses have averaged 425 *n* to two opposing fields in 45 days. The maximum given was 775 *n* to one field in 40 days. The average total elapsed time including the first and last treatment was 45 days. The shortest treatment was 12 days and the longest 61 days. The average number of treatment visits for each patient was 15, the minimum being 7 and the maximum 20 when the full courses were given. Some treatments were unduly prolonged when the apparatus was shut down for repairs. In treating the prostate cases, one anterior and two posterior fields were used but only two were treated in a single day.

The skin reactions produced varied from mild erythemas to marked epidermitis, but all to date have healed satisfactorily. In general they have tended to be dry with thick, heavy incrustations especially over the face and neck. In several cases large numbers of subcutaneous abscesses have formed. Subcutaneous edema and thickening of the tissues of the neck are constant sequelae. The anterior fields of the prostate cases showed marked *reactions* to 425 *n* in 33 days or 525 *n* in 45 days, but the gluteal fields withstood 650 *n* in 61 days. The mucosal reactions resembled those following x-ray, but have usually been patchy. The patients treated about the face and neck developed dry mouths and lost their sense of taste.

Nearly all the primary lesions have shown some regression, and when ulcerated have healed remarkably well. The metastatic glands also have regressed considerably and usually leave a smaller, hard, indurated area. Some metastatic glands have undergone necrosis. The necrotic material was usually thick and not watery.

Microscopic studies of some of the treated tissues show necrosis and fibrous reactions.

In conclusion, it is obvious that malignant tissues regress under fast neutron ray treatments. Normal tissues do not seem to be irreparably damaged by the doses necessary to produce tumor regression. Improvements in technique and operating conditions will undoubtedly produce better results. The recurrence of cancer and the rate of recovery of tissues from neutron therapy are, of course, not known at this early date.

63. Utilization of Slow Neutrons for Therapeutic Purposes. P. GERALD KRUGER, *Department of Physics, University of Illinois, Urbana, Illinois.*

Studies[1] of the effects of the disintegration products from the nuclear reaction ${}_5B^{10}+{}_0n_s'\rightarrow{}_3Li^7+{}_2He^4$, on mammary carcinoma, lymphoma and sarcoma, show that the ionization produced by these disintegration products is sufficient to cause lethal effects *in vitro*.

In the *in vitro* experiments small pieces of the neoplastic tissues were immersed in a boric acid solution and then irradiated with slow neutrons. In this way the boron nucleus is disintegrated in the environment of the tumor cells, and the dissipation of the energy of the disintegration products produces an intense ionization in the cells. After implantation in mice, the growth of the irradiated samples is compared to the growth of tumor particles immersed in boric acid solution but not irradiated before implantation. A comparison of these data with those from other experimenters using fast neutrons, shows that the lethal effects observed after the slow neutron irradiation, are produced by the boron disintegration products.

Since all elements which appear in tissue with an appreciable concentration have a cross section for slow neutron capture which is small compared to that for boron, no strong ionization can be produced in tissue by slow neutron irradiation unless boron or some other nucleus having similar characteristic is introduced into the tissue. Thus it may be expected that results similar to those observed in the *in vitro* experiments may be obtained *in vivo* if sufficient boron, in some suitable form, can be applied to tumors *in vivo*. The localization of ionization by this method, when applied to *in vivo* work, will remove the danger of skin burns and similar disturbing factors which are prevalent in x-ray, γ-ray and fast neutron therapy.

Before *in vivo* experiments of this type may be performed, with hope of success, it will be necessary for the chemist to supply the biologist or the physicist with suitable organoboron compounds, i.e., they must diffuse through tissue slowly, or be decomposed by chemical reaction in tissue in such a way as to deposit the boron in the tissue, and they must be nontoxic. Such a problem does not seem to be hopeless from the chemist's standpoint.

From the data obtained in the *in vitro* experiments it is possible to calculate the approximate amount of energy which must be dissipated in a cell or in its nucleus to cause lethal effects. The results of such a calculation indicate that approximately 650 Mev per cell or 80 Mev per cell nucleus are required to kill mammary carcinoma cells.

[1] P. Gerald Kruger, Proc. Nat. Acad. Sci. **26**, 181 (1940).

64. Intracellular Irradiation. J. H. Lawrence, L. A. Erf and L. W. Tuttle, *William H. Crocker Radiation Laboratory, University of California, Berkeley, California.*

A. *Yeast cells.*—When Baker's yeast cells (Sacch Cereviseae) were suspended for one and one-half hours at 22°C in (a) glucose-salt, (b) fluoride glucose-salt, and (c) sustaining salt mediae, to each of which radio-phosphorus ($_{15}P^{32}$) in form of phosphate had been added, radioactivity was found only in those cells suspended in the first solution. The uptake of the radio-phosphorus varied with the concentration of glucose. Once the yeast cells had incorporated P^{32}, it was not lost by resuspending the cells in a radio-phosphorus-free media. These and other experiments indicated that the curve representing the uptake of radio-phosphorus could be more or less superimposed upon the curve representing the metabolic rate of yeast cells and not upon the growth curve.

By the use of ice-cold five percent trichloracetic acid and hot ether-alcohol solutions, it was determined that approximately 80 percent of the activity was found in the acid soluble and 20 percent in the nucleoprotein fractions. (Approximately 40 percent of the activity of the nucleoprotein fraction was present in the nucleic acids.) Iodoacetic acid decreased while cyanide increased the rate of uptake of radio-phosphorus in the nucleoprotein fraction.

B. *Mouse cells.*—StrongA mice which have been inbred for nearly 80 generations and a very cellular, vascular lymphoma with lymphemic characteristics which has been transferred in about 80 generations, were used. The tumor takes in 100 percent of the mice inoculated and regressions have not been observed. After the intraperitoneal administration of radio-phosphorus to both normal and leukemic animals, the retention of activity in the whole carcass of the leukemic animals was greater than in those of normal animals during a 100-hour period. When the tissues were assayed separately, it was noted that the muscle tissue of the leukemic animals retained less activity than those of normal animals, however the bone and liver slightly more, while the lymph nodes and spleen retained much more during a period of 100 hours. These findings were thought to be due to the more rapid metabolism of the leukemic cells and to their varied infiltration in organs and tissues. The liver, spleen and lymph nodes of normal and leukemic animals were then fractionated into three broad groups of biologically active phosphorus compounds: phospholipids, nucleoproteins and acid soluble fractions. Leukemic infiltration of these organs was accompanied by an increase of several-fold in the uptake and retention of activity by the nucleoprotein and acid soluble fractions over the normal organs. The phospholipid metabolism of spleen and lymph nodes was but slightly altered by leukemic infiltration, while that of the liver was depressed the first day after administration of P^{32}.

C. *Human cells.*—With the realization that radio-phosphorus concentrated more rapidly in the nucleoprotein fraction of transmitted leukemic cells than in normal mouse cells, in addition to the marked concentration in bone and bone marrow, it would seem to be an ideal method of giving selective irradiation in leukemia. It has now been administered orally and intravenously to approximately 200 cases of leukemia, Hodgkins, myeloma, melanoma, osteogenic sarcoma, polycythemia, and to four normal individuals. The rates of absorption (blood and biopsies of various tissues) and of excretion (urine and feces) have been determined in approximately 40 cases. As was found in the mice, the greatest concentrations of activity occurred in the nucleoprotein fraction of leukemic cells, while lesser concentrations occurred in normal blood cells during a period of one week following administration. Activity assays have been made of autopsied tissues of 30 cases. In those patients to whom radio-phosphorus had been administered many days before death, the concentrations of radio-phosphorus were greatest in the osseous tissue, while in those to whom P^{32} had been administered just previous to death, the concentrations were greatest in such tissues as bone marrow, spleen and liver. This indicates that the more rapidly metabolizing tissues quickly utilize available radio-

phosphorus and that later it is probably stored as a calcium salt in the bones.

The therapeutic results were quite encouraging. In the group of 16 cases of various types of chronic leukemia untreated by any other method such as x-ray or arsenic and which have been treated with radio-phosphorus only during the past two years, only five have died, and three of these were moribund at beginning of treatment. The others continued to respond well to treatment. Advantages of this form of therapy include (1) simple method of giving localized whole body irradiation in a single cocktail or intravenous injection; (2) absence of irradiation reactions.

Radiology IV

Dosage Measurements

Chairman: DR. EDITH H. QUIMBY, *Memorial Hospital, New York*

70. Measurement of Short Wave Radiation in Roentgens. LAURISTON S. TAYLOR, *National Bureau of Standards, Washington, D. C.*

A brief review will be presented covering the more important attempts to measure megavolt x-rays and gamma-rays in roentgens. Particular emphasis is laid on the laboratory standardization measurements. The measurement of x-rays in roentgens up to 300 kv can be done in a straightforward manner involving no difficult assumptions or corrections. However, for higher excitation voltages, measuring instruments become unwieldy, with the result that indirect methods of measurement are employed. Some methods, such as those employing the thick-walled thimble chamber may involve certain assumptions as to the counter-balancing effects of different components of the ionizing radiations and absorption and scattering in the chamber walls. While such chambers are to be considered as fairly satisfactory, they cannot be considered as absolute in their measurements. Extension of the useful range of free air ionization chambers through the use of high pressures, avoids some of the assumptions involved with thimble chambers but in turn involves corrections in the current measurement itself through the presence of columnar recombination effects. Simple enlargement of the chamber dimensions may apparently avoid both of these difficulties but the chamber itself becomes so large that the exclusion of other secondary effects is uncertain. Consequently there is something to be desired in all the methods used thus far for the absolute measurement of the roentgen.

Practical measurement of the roentgen, as in water phantoms, becomes more complicated in the higher voltage and gamma-ray regions when using secondary chambers which have been calibrated under standardized laboratory conditions against some sort of primary standard. The mode of comparison with the standard is to some extent dictated by the purpose to which the secondary chamber will later be applied.

71. Determination of Energy Absorbed Per Gram of Tissue. T. N. WHITE, *National Cancer Institute, Bethesda, Maryland.*

There will be reviewed the conditions under which one may ascertain the energy absorbed in tissue in terms of the ionization which occurs in a gaseous cavity introduced into the tissue. This method has been thoroughly discussed and tested by L. H. Gray in the case of the filtered gamma-rays of radium with its decay products. Both Gray and Zimmer have given some attention to the application of the method with fast neutrons. In essence the method depends upon the behavior of ionizing particles in matter, and an attempt will be made to express the conditions which should be fulfilled without making any direct reference to the source or exact nature of the ionizing particles. The purpose of this mode of presentation is to facilitate perception of the range of applicability of the method.

The proposed conditions are summarized as follows:

(1) It must be necessary to evaluate only that energy which is absorbed in the tissue on account of deceleration by the tissue of the motion of ionizing particles.

(2) In any gas of low atomic number, the average number of ion pairs formed per small decrement of energy should be practically independent of the kinetic energy of the ionizing particles.

(3) The rate of loss of energy in tissue by the ionizing particles should bear to the rate of loss of energy in the gas of the cavity a ratio which is practically independent of the kinetic energy of the particles.

(4) On an average, the energy absorbed in the cavity from any ionizing particle must be small in comparison with the energy with which the particle traverses the cavity.

(5) The number of primary ionizing particles of any specified energy traveling in any specified direction should be practically the same at all points throughout the tissue within which the cavity is introduced.

It is considered that in any case where the above conditions hold the energy absorbed may, for practical purposes, be expressed by means of Gray's formula:

$$E = dWJ$$

where E is the energy absorbed per gram of tissue adjacent to the cavity, W is the average decrement of energy of ionizing particle per pair of ions formed in the gas of the cavity, J is the number of ion pairs formed per gram of gas in the cavity, and d is the ratio stated in (3) above (rates being expressed as energy loss per gram cm^{-2}).

The consequence of failure to meet certain of the conditions will be discussed.

Some attention will be given to the applicability of the method in cases where tissue is irradiated with an externally produced beam of ionizing particles, and where a small amount of radioactive material is uniformly dispersed in the tissue.

Insofar as time permits, pertinent data will be summarized and experimental technique will be discussed.

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72. Distribution of Ionization Produced in the Human Body by Different Methods of Irradiation. PAUL C. AEBERSOLD,* *William C. Crocker Radiation Laboratory, Physics Department, University of California, Berkeley, California.*

Nuclear physics has resulted in two new methods of irradiating lesions within the human body, the use of beams of fast neutrons and the administration of induced radioactive substances. Comparisons of the distributions of ionization produced in the human body by these new methods with those achieved by x-ray and radium irradiation are being made in our laboratory by means of both physical and biological tests. Comparisons have also been made of the distributions produced by different qualities of x-rays applied in various ways.

As yet it is not possible for all qualities and kinds of radiation to give absolute values of the energy expended in ionization at points in a body, i.e., absolute tissue dosage. However, an approximation to the tissue dose can be attained under certain conditions by measuring the ionization produced in a tiny gas cavity or chamber of special properties introduced in the body and then applying the Bragg-Gray relationship for the ionization in such a cavity. The validity of this procedure for x-rays, gamma-rays and fast neutrons will be considered. For administered radio-elements that emit only beta-rays, the absolute energy expended per unit volume of tissue can readily be calculated if the average energy of the emitted beta-particles is known and an assay is made to determine the number of particles emitted in the unit volume. In general there are uncertainties in these determinations that will need to be cleared up before absolute dosages can be stated for this type of irradiation, but in most cases good approximations can be made.

Assuming that a distribution of ionization can be measured that will approximate tissue dosage, it is nevertheless inadequate to compare a few such physical measurements, e.g., percentage depth doses, in comparing the relative efficacy of one type of irradiation over another. The density of ionization along tracks of secondary protons resulting from neutron irradiation is very different from that along electron tracks resulting from x- and gamma-irradiation, and it will vary with the energy of the neutrons. Also radio-elements may deposit selectively in certain cells, or even in parts of cells, and give rise to a submicroscopic picture of ion distribution different from that occurring under x-irradiation. The different submicroscopic distribution of ionization resulting from the use of these new irradiation methods can produce different biological effects even when the physical measurement of volume ionization is the same. Consequently, before the ordinary volume ionization measurements can be used for indicating relative biological depth doses the relation between the ionization measurements, and the biological effects sought must be investigated over the range of qualities acquired by the radiation in the body. Moreover, the relative recovery factor of different tissues, such as normal and neoplastic tissue, may be different for neutrons than for x-rays. Also, the relative recovery of tissues must be considered for the slow rate of dosage that can be used with administered radio-elements.

Although no such exhaustive investigations have yet been made, tests show that the depth doses achieved by the fast neutron beam of the 60-inch cyclotron are as good as those achieved by high voltage x-rays, and this is born out by clinical observations. Also clinical results on patients administered radio-elements show selective radiation effects found from physical and biological tests. It appears that these new methods of irradiation may be favorable adjuncts to present radiation therapy.

* Fellow of the Finney-Howell Research Foundation.

Radiology V

Radiobiology

Chairman: DR. CHARLES PACKARD, *Columbia University*

76. The Relation of Tissue Phosphatase to the Deposition of Radioactive Phosphorus in Bone Tumors. HELEN QUINCY WOODARD, *Memorial Hospital, New York, New York.*

When radioactive phosphorus enters the body it is held temporarily in high concentration in storage organs such as the liver. After a variable period of storage it is released for metabolism in other regions. Since all tissues contain phosphorus, the radioactive isotope, like the normal one, is taken up to replace catabolized material and to build new. The rate of uptake by different tissues depends on their phosphorus content and rate of metabolism. The phosphorus content of bone is high, and bone produces an enzyme, alkaline phosphatase, which aids in making phosphorus available for deposition as calcium phosphate. Hence available supplies of radioactive phosphorus tend to

localize in the skeleton. Bone tumors which are growing rapidly and have the capacity to calcify contain abundant phosphatase. In these tumors, as in normal bone, the rate of deposition of radioactive phosphorus usually is a function of the phosphatase activity. Many, although not all, of the metastases from bone tumors have the same high phosphatase activity as the primary lesions. There is a tendency for radioactive phosphorus to localize in these metastases. Radioactive phosphorus thus appears likely to be a valuable therapeutic agent in the treatment of phosphatase-producing bone tumors. It may prove to be useful as an adjuvant to external irradiation of the primary tumor. It may also be found to be effective as a prophylactic agent to inactivate metastatic deposits before they become established. As alkaline phosphatase usually appears in large quantities in the serum of patients with phosphatase-producing tumors, the serum phosphatase readings may be taken as an indication of the suitability of a patient for radioactive phosphorus therapy.

This work was carried out in cooperation with Mr. L. Marinelli and Dr. John Kenny of this Hospital. The radioactive phosphorus was obtained through the courtesy of Dr. E. O. Lawrence of the University of California.

77. Some Experiments on the Localization of Lithiated Dyes in Tumor Tissue and Their Bearing on the Possibility of Slow Neutron Therapy. PAUL A. ZAHL AND F. S. COOPER, *Memorial Hospital, New York, New York; The Haskins Laboratories, New York, New York.*

In a paper by Zahl, Cooper and Dunning[1] experiments were described in which mouse sarcomas were injected hypodermically with slowly diffusing suspensions of boron or lithium salts and then subjected to slow neutron irradiation. Resulting tumor regressions were considered to be due to the nuclear capture reactions which occur between lithium or boron atoms and slow neutrons with the release of very high energetic particles. However, for the possible utilization of this nuclear reaction in the clinical treatment of cancer, hypodermic injection of lithium or boron materials is not considered feasible. The authors have therefore interested themselves in seeking other devices for localizing slow neutron capturing materials in tumor tissue.

It has been found that certain diazo dyes (most of which are sodium salts of the disulphonic acid complex) have the property when injected intravenously of localizing in greater concentration in tumor tissue than in normal tissue. Similar salt dyes were prepared in which lithium (because of its proximity to sodium in the alkali series) replaced the sodium. Such lithiated dyes were injected intravenously into tumor-bearing mice, and after suitable periods quantitative spectroscopic analyses for lithium content were made on the tumor tissue as well as on the other tissues of the body. Similar tests were made using simple binary lithium salts.

It was found that considerably more lithium accumulates in the tumor tissue than in the normal tissues. The accumulation occurs rapidly, reaching a maximum at between four and seven hours following injection. The maximum concentration is sustained for a relatively short period and is followed by slower drainage and excretion. At between 24 to 48 hours after injection lithium is no longer detectable in the system. Maximum concentrations attained in tumor tissues ranged at 0.03 percent of elemental lithium for wet tissue. The concentration of lithium in the tumor tissue was approximately twice that found in the liver and kidneys, and an even higher differential exists for the other tissues.

Results to date of this work will be presented together with a discussion of the implications of differential localization of slow neutron capturing materials considered in relation to the problem of cancer treatment with slow neutrons.

[1] Zahl, Cooper and Dunning, Proc. Nat. Acad. Sci., October, 1940, in press.

78. Relative Effect of X-Rays on Resting and Actively Secreting Kidney Tubules. ROBERT CHAMBERS, *New York University, New York, New York.*

The investigation was made on explanted fragments in tissue culture of the chick mesonephric proximal tubules. The cut ends of these tubular segments heal over in a few hours and the closed segments continue to function, their lumina becoming distended with a fluid secretion. In the usual plasma medium of the culture the distension is relatively slow but, when phenol red is added to the medium, the distension is accelerated, the lumina becoming intensely colored with phenol red. $MgSO_4$ was found to have a similar effect of inducing distension. The difference in the rate of distensibility of the tubules was taken as a criterion for the active and relatively inactive state of the secretory cells in the walls of the tubules.

Explants of the tissue cultures of 48 hours incubation were exposed to x-rays of various intensities and the effect of the irradiation noted on the ability of the closed segments of the tubules to become distended with secretory fluid.

The tubules in the explants were found to be extraordinarily resistant to irradiation, the tubules being able to accumulate phenol red in the normal manner if the phenol red is added at any time after an irradiation dosage of 25,000 roentgens. With dosages from 40,000 to 60,000 roentgens evidences of deterioration appear after about 50 to 60 hours of incubation and within 5 days the majority of the proximal tubules have undergone necrosis. However, the few which remain intact appear as healthy as the controls and equally able to accumulate phenol red.

Within the 50 to 60 hours after an irradiation of as high as 60,000 roentgens the addition of phenol red to the medium at varying times shows that the tubules develop progressively increasing ability to function normally in the accumulation of phenol red in their lumina. Thus, 3 hours after the irradiation the pick-up is much less than that of the controls, at 20 hours it is improved and at 28 hours it is at its best. Later, the number of healthy active tubules diminishes, until at 5 days there are very few, but the few tubules which have survived are as good as the controls.

There is a marked difference in the susceptibility of the tubules to irradiation according to whether the tubules are

irradiated in the presence or in the absence of secretion inducing substances, e.g. phenol red or $MgSO_4$. The normal culture medium for these tubules was blood plasma which, apparently does not contain substances to be secreted in sufficient quantity to induce more than a mild activity of the tubular cells. On the other hand, when phenol red or $MgSO_4$ is added to the medium the cells of the proximal tubules are greatly stimulated to activity and distension of the tubules is accelerated. Under these conditions the toxic effect of the irradiation is more pronounced. The tubules start to distend but in a few hours undergo progressive degeneration which, several days later, becomes wide spread.

In conclusion, these experiments indicate that healthy, "resting" proximal tubules of the chick mesonephros in tissue culture are far less susceptible to the toxic effects of x-rays than when the tubules are being stimulated to accelerated secretory activity during the irradiation.

Tubules, irradiated in the "resting" condition, require time to recover from the effects of the irradiation. If the tubules are stimulated to secrete at or within a few hours after being exposed to x-rays they tend to succumb. On the other hand, the longer they are allowed to remain in the "resting" condition after the irradiation the better able are they to resume functional activity.

79. Some Effects of Germ Cell Injury Produced by X-Rays. PAUL S. HENSHAW, *Research Fellow, National Cancer Institute, Bethesda, Maryland.*

How radiation acts on the cells of living matter to bring about biologic change and cell death is of importance not only in the treatment of malignant disease and the understanding of general biologic behavior but also in the protection of the offspring of those who work with radiation. Information bearing on these points may be obtained from a study of the injury induced in germ cells by x-rays.

Recently it has been our privilege to observe irradiation changes produced in a number of kinds of sperm and ova (the gametes of the marine worm, *Nereis limbata;* the marine clam, *Cumingia tellinoides;* the fly, *Drosophila melanogaster;* the sea urchin, *Arbacia punctulata;* and the common frog, *Rana pipiens*). In general the procedure was to expose one or the other gamete to x-rays, after which fertilization was allowed to occur and subsequent behavior observed.

It was found, (1) that without exception the motility of sperm and their ability to activate the ovum was not impaired by doses of radiation far in excess of those which would cause extensive abnormalities in later development; (2) that in one case (*Nereis*) extensive swelling of the fertilization membrane occurs when the ovum is exposed to the radiation; (3) that delay in cell division and interrupted phase relationship of cleavage mitoses occurs in sea urchin material when either gamete is treated; (4) that in the sea urchin material, multipolar cleavage may be induced by the exposure of either gamete to a dose of around 20,000 r (observations (3) and (4) will be illustrated by moving pictures); and (5) that in the case of both frog and *Drosophila* material quite normal cell proliferation and cleavage may be observed after exposure of sperm to radiation, whereas little or very abnormal differentiation is found to occur.

These findings indicate (a) that injury of a variety of types (sometimes extensive as death) may be transmitted to offspring by changes produced in mature sperm or ova by high energy radiation; (b) that extensive abnormalities in development may result from irradiation changes produced in what is essentially half a normal cell nucleus—a sperm; and (c) that since abnormal distribution of chromatin material resulting from multipolar cleavage usually leads to cell death, this may be pointed out as one means by which radiation causes death in cells.

80. Effects of High and Low Temperatures During Roentgen Irradiation on the Susceptibility of Skin of Young Rats. TITUS C. EVANS, *Departments of Radiology and Zoology, State University of Iowa, Iowa City, Iowa.*

One-day old rats were irradiated at 0–5°C and at 30° with dosages ranging from 300 to 3000 roentgens. In all cases it was found that the skin of the rats irradiated at the higher temperature was injured more than that of the rats treated at 0–5°. The animals were kept at these temperatures only during the time required to give the x-ray treatment.

The radiation (130 kv, cardboard filter only) was delivered at an intensity of 100 r per minute. The experiments were begun with a treatment of three minutes and in each following experiment the dosage was increased by 300 r.

The young rat was taped to a sheet of lead containing a 2×4 mm port which was placed over the region to be irradiated. The animals were kept near 0° during the irradiation by packing snow or crushed ice around them. Immediately after the treatment the animals were placed at 30° and as soon as they regained their ability to breathe and move, they were placed back in the cage with the mother. In each experiment a litter-mate of the same size and sex (only males were used) was irradiated at 30° and moist cotton was substituted for the snow. Controls were kept at 0–5° and at 30° during the time the experimentals were being treated. Only periods of 30 minutes at 0° appeared to be near the limit of endurance, and once a rat resumed breathing the recovery was complete.

The animals were killed and photographed when they were two weeks of age. The injury was evident externally by the degree of epilation produced. In all experiments the epilation was more severe in the animal irradiated at 30° than in the one treated while cold. A dosage of 3000 r was required to produce an area completely devoid of hair whereas a treatment of only 1000 r had the same effect on exposed skin of the animal irradiated at the higher temperature.

Histological examination revealed even more of a difference in the effect produced at the two temperatures. At the lower temperature 3000 r of radiation did not destroy many of the deeper follicles and very little tissue reaction was apparent. The effect of the same dosage at the higher temperature was extreme. Not only was complete epilation and excessive desquamation evident, but the epidermis exhibited injury closely resembling hyperkeratosis. The slight tissue injury of the skin irradiated at the low temper-

ature was comparable to that of the rat treated with only 300–600 r at 30°.

This biological material is peculiarly well fitted for a demonstration of this kind. The metabolism of rats of this age is inhibited quickly and perhaps completely by low temperature. The skin is relatively undifferentiated and growth is rapid. Thus metabolism and cell division were at a minimum during the irradiation at 0–5° and were near a maximum during and following treatment at 30°.

81. The Effect of X-Rays on Bacteriophage. FRANK M. EXNER, *Department of Cancer Research,* AND HELEN ZAYTZEFF-JERN, *Department of Surgery, Columbia University, New York, New York.*

The rate of inactivation of a virus by x-rays gives a basis for calculating the size of the radiosensitive portion of the virus corpuscle for comparison with the size given by ultrafiltration and ultracentrifuge methods. The calculation is based on the so-called "hit" theory. Application of this theory to these simplest known self-reproducing entities should help in determining the extent to which the theory is applicable in other biological problems.

While plant viruses have been employed in x-ray investigations for some time (Gowen), a definite action of x-rays on bacteriophages (viruses parasitic on bacteria) has only recently been reported.[1] The work here described represents an independent investigation of the suitability of bacteriophages for x-ray studies.

The effect observed was the x-ray inactivation of bacteriophage corpuscles suspended in 1 percent yeast extract broth containing 0.5 percent NaCl, *p*H 7.6 to 7.8. Concentrations of about 10^9 corpuscles per cm^3 were employed. Anticoli and antistaphylococci bacteriophages were used with their homologous strains of bacteria.

To determine the concentration of corpuscles high decimal dilutions of bacteriophage suspension are made and mixed with an optimum number of the homologous strain of bacteria. 0.01 cm^3 portions of these mixtures are evenly spread on 1 percent agar plates. After incubation clear spots (plaques) in the otherwise uniform bacterial growth represent colonies of bacteriophage derived from individual corpuscles, which can thus be counted.

X-ray dosage measurements are based on a Victoreen ionization chamber. Corrections including absorption and scatter probably total under ±15 percent and are omitted.

Most of the exposures were made at the rate of about 1000 r/min. with copper half-value layer of 3.5 mm corresponding to about 425 kv on a tungsten target, with 0.6 mm copper filtration.

The ratio N/N_0 of corpuscles surviving exposure was followed from unity to about 10^{-6}. Over this range the data fit well on a curve $N/N_0 = e^{-\alpha q}$ where q is the dose in r. The value of α is 2.5×10^{-5} r^{-1} for the staphylococcus and 3.0×10^{-5} r^{-1} for the B. coli bacteriophage.

This great range of exponential inactivation, together with a number of special tests, points to a direct action of the radiation on the bacteriophage as against an indirect action through the medium.

The volume of the radiosensitive portion of the corpuscle is obtained from the probability α that this volume will be "hit" by an exposure of 1 roentgen. This requires a knowledge of the number of ion pairs per hit. From the known gross size of bacteriophage corpuscles it is apparent that in this case the clusters of secondary ionization along the recoil electron tracks (3 ion pairs per average cluster) will act as units.[2] Omitting minor correction factors which tend to cancel, a mean diameter for the two bacteriophages comes out 4.5×10^{-6} cm (45 mμ) in agreement with the range of sizes (50–80 mμ) obtained with related strains of bacteriophages by filtration and centrifuge methods.

One experiment with 200 kv x-rays showed no significant difference from the harder radiation. This is contrary to unpublished results with tobacco mosaic virus (J. W. Gowen and F. M. Exner).

Irradiation of these materials with fast neutrons is planned with the hope of helping to clarify the rôle of ion distribution in different types of biological response to radiation.

[1] E. Wollman and A. Lacassagne, Ann. de l'Inst. Pasteur **64**, 5 (1940). E. Wollman, F. Holweck and S. Lauria, Nature **145**, 935 (1940).
[2] D. E. Lea, J. Genetics **39**, 181 (1940).

General I

Production of Radioactive and Stable Isotopes and of Penetrating Radiations

Chairman: DR. EDW. U. CONDON, *Westinghouse Research Laboratories*

46A. The Production of Neutrons and Artificial Radioactivity. M. A. TUVE, *Department of Terrestrial Magnetism, Carnegie Institution of Washington, Washington, D. C.*

Information and personal opinions are being collected on the points indicated in the following outline, with particular reference to obtaining active discussion and arriving at a reasonable estimate of the present situation relating to the average operating performance and costs of nuclear physics laboratories.

Outline

(A) Introduction

Spheres of usefulness of the electrostatic generator, and the cyclotron: General comments

(1) Voltages and currents
(2) Yields of neutrons and artificial radioactivity
(3) Advantages of each for special purposes
(4) General cost comparison
(5) Radium comparisons

(B) Neutrons

- (a) *Nuclear reactions of most use*
- (b) *Intensities obtained*
  - (1) Electrostatic generators now in operation
  - (2) Small cyclotron
  - (3) Medium-size cyclotrons in operation at various institutions
  - (4) Large cyclotron (60-inch)
  - (5) Possible extensions of each technique
- (c) *Qualifications on these intensities*
  - (1) The need for and disadvantages of intensity monitors
  - (2) Total flux of neutrons *versus* useful flux for various cases
  - (3) Fast neutrons; energy and space distributions
  - (4) Slow neutrons; useful flux, collimation, fast neutron accompaniment, blur of source
  - (5) Homogeneity of energy
  - (6) Modulated neutron source for mono-energetic slow neutrons; energy range available now; possible extensions of this technique
- (d) *Neutron sources for biological use*
  - (1) Victoreen units (Zimmer, Gray, Aebersold)
  - (2) Intensities used or needed
  - (3) Practical considerations; collimation, time schedules, operating reliability

(C) Artificial radioactivity

- (a) *Important radioactive elements and reactions; typical uses to date, and amounts required*
- (b) *Electrostatic generators*
  - (1) Yields obtained; voltages and currents used
  - (2) Use of weak sources for laboratory studies
  - (3) Indirect production using neutrons
  - (4) Costs
- (c) *Cyclotrons*
  - (1) Yields; comparison of production by direct bombardment and by absorption of neutrons
  - (2) Actual amounts produced in various laboratories; maximum; usual; average; over-all production during one or two years past; typical sources available
  - (3) Costs per millicurie; direct costs; costs allowing for time of staff and losses of operating time; over-all costs, including overhead and depreciation
- (d) *Possible extensions of these techniques*
  - (1) Electrostatic generator; developments and expectations
  - (2) Cyclotron; developments and expectations
- (e) *Chief troubles*
  - (1) Electrostatic generators
  - (2) Cyclotrons

(D) Cost Data

- (a) *Electrostatic generator*
  - (1) Capital investment and construction time to useful operation
    - (a) Open air type generators
    - (b) Small pressure type generators
    - (c) Large pressure type generators
    - (d) Building space costs
  - (2) Maintenance and improvement costs; staff; running costs
  - (3) Percentage of operating time; reliability; discounts
  - (4) Best present judgment for a recommendation now
- (b) *Cyclotron*
  - (1) Capital investment and construction time
    - (a) Small
    - (b) Medium, 32-inch to 45-inch units
    - (c) Large, 60-inch and up
    - (d) Building space costs
  - (2) Maintenance and improvement costs; staff; power; repairs and replacements; supplies; institutional costs
  - (3) Percentage of operating time; reliability; dependence on objectives and changes

(E) Reasons given for installing nuclear physics equipment

- (a) *Teaching laboratories; supply and demand*
- (b) *Research laboratories in physics; industry*
- (c) *For fundamental research in biology and chemistry*
- (d) *For medical studies and use*

The above outline covers the topics indicated by others as desirable for this discussion, particularly with reference to anticipated future equipment. The topics which actually will be covered are to be determined by the group present. Vigorous discussion and contribution by those present is expected.

46B. The Production of Neutrons and Artificial Radioactivity.* M. S. LIVINGSTON, *Massachusetts Institute of Technology, Cambridge, Massachusetts.*

Representatives of various laboratories have contributed data pertaining to the yield of neutrons and P^{32} radioactivity from disintegration apparatus, and also installation and operation costs. These data are tabulated in Tables I and II. For comparison with neutron therapy costs data from x-ray and radium-pack installations have been included. The headings are as follows:

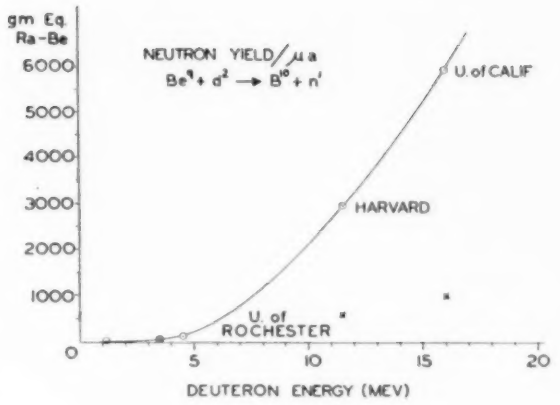

FIG. 1.

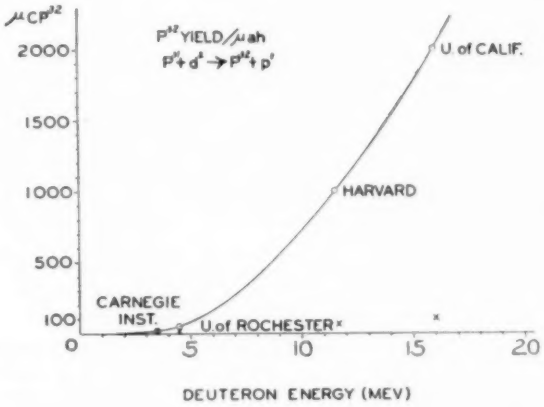

FIG. 2.

1. Installation.
2. Size: pole face diameter for cyclotrons, sphere diameter and air pressure for electrostatic generators.
3. Energy (Mev): working energy for deuterons or electrons, in million electron volts.
4. Installation cost: complete replacement cost including apparatus, housing, shielding and salaries of technical and supervisory staff during construction.
5. Operations crew: supervisory and technical staff required for operation and maintenance.
6. Operating cost/yr.: salaries for operations crew, overhead and maintenance costs, 4 percent interest on capital investment, 10 percent building depreciation and 20 percent apparatus obsolescence charge per year.
7. Average operation: except where noted an average figure of 7 hr./day, 2400 hr./yr. has been used to compare relative costs, due to present lack of performance data.
8. Operating cost/hr.
9. Deuteron beam (μa): the figures in parentheses are estimates of a proper yield for instruments not fully developed for quantity production, as indicated by results in other laboratories. For the x-ray installation electron currents in microamperes are used.
10. Operating cost/μa hr.
11. μa hr./mC P^{32}: reported deuteron bombardment in microampere hours to produce one millicurie of P^{32} from P (d, p) reaction. Figures in parentheses are estimates or produced by slow neutrons.
12. Cost/mC P^{32}.
13. Neutron intensity: reported fast neutron intensity in the forward direction per microampere of deuterons in terms of that from 1 g Ra mixed with Be.

TABLE I. *Cyclotrons.*

		LARGE 16 MEV	MEDIUM 8–12 MEV	SMALL 3–7 MEV	BABY 1–2 MEV
1.	Typical installation	U. of Calif.	Harvard & M.I.T.	Rochester	Cornell
2.	Size	60 inch	42 inch	27 inch	16 inch
3.	Energy (Mev)	16	11.5	4.5	1.4
4.	Installation cost	$182,000	$60,000	$25,000	$6000
5.	Operations crew	15	6	7	2
6.	Operating cost/yr.	$60,500	$25,000	$20,000	$5000
7.	Average operation (hr./day, hr./yr.)	(7/2400)	(7/2400)	(7/2400)	4.5/1500
8.	Operating cost/hr.	$25.20	$10.40	$8.30	$3.33
9.	Deuteron beam (μa)	200	20 (100)	4 (50)	25
10.	Oper. cost/μa hr.	$.125	$.52 ($.104)	$2.07 ($.166)	$.133
11.	μa hr./mC P^{32}	5	10	(200)	(750-*n*'s)
12.	Cost/mC P^{32}	$.625	$5.20 ($1.04)	($207) ($16.60)	$100
13.	Neutron intensity (g Ra-Be Eq./μa)	6000	3000	(200)	40
14.	Effective neutron int. ("*n*" units/min. @ 100 cm)	7.5	0.38 (1.9)	(0.005) (0.0625)	0.006
15.	Cost/"*n*" unit of *n*'s	$.056	$.47 ($.087)	($28) ($2.20)	$9.25
16.	"*r*" units/min. (for therapy)	30 @ 100 cm	1.5 (7.5)	(0.02) (0.25)	
17.	Therapy cost/100 "*r*"	$1.40	$11.50 ($2.30)	($690) ($55)	

TABLE II. *Electrostatic generators.*

	PRESSURE 3–5 MEV	LARGE AIR 2–3 MEV	SMALL AIR 1–2 MEV	X-RAY 1 MEV	RADIUM BOMB
1.	Carnegie	M.I.T.	Carnegie	Mass. Gen. Hosp.	Memorial Hosp.
2.	18′ @ 50 lb.	15′ @ atmos.	8′ @ atmos.	2′ @ 150 lb.	4 g radium
3.	3.5	2.5	1.2	1.25	
4.	$75,000	$45,000	$7500	$20,000	$100,000
5.	3	3	3	1	1
6.	$20,000	$17,000	$3800	$6500	$4000
7.	(7/2400)	(7/2400)	(7/2400)	7/2170	16/5500
8.	$8.30	$7.10	$1.60	$3.00	$.73
9.	15 (50)	500 elect.	10	500 elect.	
10.	$.55 ($.17)	($.014)	$.16	$.006	
11.	1000				
12.	$550 ($170)				
13.	100		7		4
14.	0.02 (0.07)		0.0008		0.00005
15.	$6.90 ($2)		$33		$240
16.	0.08 (0.28)	250 @ 100 cm		50 @ 70 cm	5 @ 10 cm
17.	$17 ($6)	$.05		$.10	$.24

14. Effective neutron intensity: conversion from g Ra Be equivalent to ionization in a Victoreen 100 r thimble chamber on the basis of the Carnegie Institution's corrected figure of 0.005 "*n*"/min. at 5 cm. Neutron yields in the forward direction from cyclotrons are reduced by a factor of 4 to give the average or effective intensities.
15. Cost/"*n*" unit of neutrons.
16. "*r*" units/min.: to compare therapy costs of neutrons, x-rays and gamma-rays, neutron "*n*" units are multiplied by a factor of 4, an average value for their relatively greater biological efficiency.
17. Therapy cost/100 "*r*" units.

The yields of neutrons per microampere in the Be (d, n) reaction and of P^{32} radioactivity per microampere hour in the P (d, p) reaction are plotted against deuteron energy in Figs. 1 and 2. Although the relative accuracy of points on the curves may be poor, these excitation functions show a more rapid increase with energy than would be expected on the basis of the increased penetration of deuterons into the target. Increase in yield due to range alone would vary with $E^{\frac{1}{2}}$. The points indicated by crosses are computed for this variation from the value at 3.5 Mev.

* This paper was substituted for 46A, originally scheduled for this place in the program.

47. The Separation of Stable Isotopes. HAROLD C. UREY, *Department of Chemistry, Columbia University, New York, New York.*

In the separation of the isotopes of elements other than hydrogen which will not be discussed, all methods which have been used have certain similarities. In one way or another countercurrent streams of compounds containing the element to be separated, having different isotopic compositions, are established. The differences in composition are produced by rather widely different methods. These may be listed as follows: (1) Diffusion through porous membranes or gaseous substances, (2) the differences in composition produced by thermal diffusion, (3) differences in composition produced by differences in chemical and physical properties, such as exchange reactions and distillation.

Very marked changes in the relative abundances of isotopes were produced by the two varieties of Hertz diffusion method. In the first of these, diffusion takes place across a solid membrane, and in the second, through moving gas streams. The speed of these methods is limited by the speed with which diffusion through porous membranes or gas can take place, which is relatively slow in the first case, since the membrane must support the difference in pressure on the two sides. This method has been used to produce very substantial separations of the neon isotopes, and some separation of the carbon and nitrogen isotopes.

The thermal diffusion method introduced by Clusius and Dickel is probably the simplest, from the standpoint of operation, of any method that has so far been devised. In this case use is made of the difference in composition established between a hot and a cold wall, provided the law of force between the molecules does not approximate closely to the inverse fifth power law, in which case no

effect is secured. If vertical heated and cooled walls are placed near each other convection is set up, and a stream having an increased concentration of the heavy isotope moves downward while a stream having increased concentration of the light isotope moves upward. Large concentration differences can be secured in this process with lengths of tube which are easily constructed and maintained in scientific laboratories. The method is applicable to a wide range of substances, depending only upon the necessity of securing the substances in a gaseous form, the substances being stable when heated, and not reacting with the walls of the vessel. The theory of this method has been given in detail by Furry, Onsager, and others. The method has been applied to secure practically complete separation of the chlorine isotopes and to secure substantial separation of the carbon isotopes and, perhaps, others.

The chemical distillation methods depend upon differences in composition resulting from slight differences in the chemical and physical properties of isotopic compounds. In these cases differences in composition between two phases are established, and the two phases are then transported relative to each other in a suitable apparatus. The systems used so far consist of: gas-liquid systems where the usual type of distillation column is used, the liquid-liquid systems used in the case of concentration of lithium isotopes by exchange between a mercury amalgam and an alcohol solution of the lithium salt, and between solid-liquid systems using zeolites and salt solutions for partial separation of the isotopes of lithium, potassium and nitrogen.

There are certain important features of all of these methods which must be considered in order to decide which is the best for a given situation. Important factors to consider are: (1) The change in concentration that can be secured in a given apparatus, (2) the time that it will require the apparatus to come to a steady state so that the maximum concentration can be produced, and (3) the rate of production of the isotopic concentrate.

All methods mentioned can produce desirable changes in concentration of isotopes. Thermal diffusion or Hertz diffusion systems can be expected to come to equilibrium in the course of hours or, at most, a day or so. The chemical and distillation methods require weeks to reach the final steady state because of the larger amount of working material in the system.

In general, it can be said that the Hertz diffusion methods or the thermal diffusion methods can produce in the neighborhood of 1–10 milligrams per 24 hours of such a constituent as C^{13} in the usual sized apparatus. The chemical methods are capable of producing about one gram of material per 24 hours. Thus, in the region where the chemical methods will work, and if isotopes are needed for experiments on a rather large scale, they are the best. This includes oxygen, nitrogen, carbon and sulfur at the present time. However, the use of the chemical method is strictly limited to elements of low atomic weight, and hence the thermal diffusion method is particularly good for elements of high atomic weight or in cases where only small amounts of material are required for experiment.

The mass spectrograph method of separation is capable of producing only small amounts of material, and cannot be considered seriously as a method for securing tracer materials. The ultracentrifuge method, on which preliminary experiments have been made, is too much in the development stage for one to be able to make any predictions. It would seem doubtful that this method will be as good as thermal diffusion because of the expensive character of the apparatus required.

48. Production of High Voltage X-Rays. JOHN G. TRUMP, *Department of Electrical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts.*

A brief discussion will be given of those properties of high voltage x-rays which account for the present tendency toward higher voltages for therapy and for industrial radiography. Several types of x-ray installations in the million-volt range which have appeared in recent years will be reviewed. It appears that the compressed-gas-insulated low frequency resonance transformer and the constant-potential Van de Graaff electrostatic generator are the most compact and economical voltage sources for the production of very penetrating x-rays. The operating principles and essential features of both these voltage sources will be discussed. Because of the low current capacity inherent in the method, the electrostatic generator is limited to the higher voltages but is relatively free from an upper voltage limit. Hospital installations of both types of x-ray generators have been made, and preliminary evidence indicates effective and reliable performance under continued use. Further gains in compactness and simplicity, arising both from improved design and from more effective insulation, are expected. An account will be given of work now under way directed at greater compactness and portability in million-volt units, as well as at the extension of such x-ray sources to several megavolts.

General II

Measurement of Radioactive and Stable Isotopes and of Penetrating Radiations

Chairman: DR. K. T. BAINBRIDGE, *Harvard University*

49. Measurement of Relative Abundances of Stable Isotopes. ALFRED O. NIER, *Department of Physics, University of Minnesota, Minneapolis, Minnesota.*

The use of separated, stable isotopes of elements such as carbon and nitrogen as tracers in chemical and biological problems requires rapid and accurate measurements of relative abundances. One of the most effective methods of making these measurements is by means of the mass spectrometer.

Various types of mass spectrometers can be employed in this type of work. Large solenoids, electromagnets and permanent magnets have been used to produce the magnetic fields needed in these instruments. A discussion will be given of the relative advantages and disadvantages of the various instruments.

Special attention will be paid to the control equipment and power supplies needed. Difficulties encountered in operating mass spectrometers will be discussed. Slides will be shown.

50. The Measurement of Radioactive Isotopes. ROBLEY D. EVANS, *Department of Physics, Massachusetts Institute of Technology, Cambridge, Massachusetts.*

For reasonably strong samples an electroscope is usually the simplest and most rugged detection apparatus, although care must be taken to avoid the temperature fluctuations to which electroscopes are usually sensitive. Prompt discrimination can be made between alpha-, beta-, and gamma-rays by means of filters. The limiting sensitivity of the best electroscopes usually lies near 10 beta-rays of about 1 Mev energy entering the electroscope per second. The more complicated ionization chamber and vacuum tube electrometer combinations offer a somewhat higher ultimate sensitivity, and are easily adapted to photographic registration. The use of pressure ionization chambers and observations by the rate-of-drift method give this combination about 5 to 10 times the sensitivity of the best electroscopes. Maximum sensitivity, for the detection of beta- and gamma-rays, is offered by Geiger-Müller discharge counters. These are about 20 times as sensitive as the best electroscopes. For gamma-ray detection screen-cathode counters are several times as sensitive as solid-cathode counters. For the detection of soft beta-rays, the sample must either be placed inside the vacuum jacket of the counter, or a very thin window must be provided in the counter jacket. S. C. Brown has shown that counters filled with helium, or helium and alcohol vapor, may be operated easily at atmospheric pressure. In this case windows may be made very thin or even eliminated entirely. A wide variety of amplifier and recorder circuits is available for discharge counters. Deviations from exact linearity of response are most readily evaluated by observations on the additive effects of a group of constant gamma-ray sources. Recording systems for low counting rates (10 to 100 per minute) usually employ a message register. For high counting rates a scaling circuit is used, or the scaling circuit and message register may be replaced by a counting rate meter whose output may be easily recorded photographically. Observational uncertainties due to purely random fluctuations in the counting rate are inherent in all measurements and cannot be reduced by the choice of amplifier circuit. Measurements on weak sources (down to 10^{-12} curie) emitting alpha-rays may be made readily with either ionization chambers, or for slightly higher sensitivities, with pulse counters employing a vacuum tube electrometer or a linear amplifier. Detection arrangements depend on whether the sample is gaseous, liquid, or solid. In every case it is essential to provide a reproducible geometry of source, windows, and detector, so that strictly comparable observations may be obtained on the background, the source, and the radioactive standard to which the activity of the unknown source is referred. The National Research Council's Committee on Standards of Radioactivity is preparing standards for use in all types of radioactivity studies. Standard radium solutions, and absolute standards of gamma-ray intensity, varying from 0.1 to 100 micrograms of radium gamma-ray equivalent, are now available through the National Bureau of Standards. Absolute beta-ray standards are also being prepared.

51. Measurements of Neutrons. J. R. DUNNING, *Department of Physics, Columbia University, New York, New York.*

Neutron investigations at present are principally concerned with the energy spectrum ranging approximately from 0 to 20 Mev. In general, most measurements involve a determination either of the absolute or the relative number of neutrons per second which pass through a given area, and which have energies within some more or less definite band. No one technique is applicable to the entire spectrum.

"Fast" neutrons with energy greater than 50 kev are effectively detected through the ionization produced by projected nuclei. Various types of ionization chambers, when connected to linear amplifiers which in turn operate scaling mechanical recorders or photographic oscillographs, provide the most satisfactory methods for measuring both neutron flux and neutron energy distributions. Proportional counters are useful where pulse size is not important. Under proper conditions, cloud chambers and also photographic plates possess some advantages for determining momentum and energy of individual neutrons.

Ionization chamber-electroscope systems which respond to integrated general ionization, and also photographic plates, are convenient for such work as neutron therapy, but the contribution of gamma-rays is difficult to determine, and quantitative interpretation not always readily possible.

Isotopes which become radioactive through n-p, n-α, or n-$2n$ reactions are often useful for selective detectors, since in general each type of reaction responds only to neutrons above some threshold energy. When more than one reaction occurs with a given isotope, or when more than one isotope is present, the interpretation must be made carefully.

No very satisfactory methods exist for neutron detection in the intermediate region from 1 to 50 kev as yet, but proportional counters, secondary emission multipliers, and some radioactive detectors offer possibilities.

The spectral distribution of the so-called "slow" neutrons which have diffused through hydrogenous material is approximately that of a Maxwell distribution appropriate to the temperature of the material, and a high energy tail in which (above 1 ev) the number of neutrons per unit energy interval should be proportional to $1/E$. The neutron capture processes in Li and B obey the $1/v$ law and yield energetic heavy particles. When connected to linear amplifier-recording systems, ionization chambers lined with these elements or filled with BF_3 gas under pressure provide very satisfactory detectors, especially for neutrons in the thermal region, from 0 to 0.2 ev. Proportional counters using BF_3 at reduced pressure posses excellent stability but are less sensitive. Neutron beams collimated by B, Cd and paraffin may be used with cyclotrons or other artificial sources for precision experiments when used with an integrating monitor system having accurately parallel characteristics. The general problem of absolute neutron flux determinations and of precision monitoring will be discussed.

Elements such as Rh, In, U, I, Br, and others which become radioactive through resonance neutron capture over a comparatively narrow energy band (or bands) serve as excellent selective detectors and filters. Collimated neutron beams using shielding of paraffin +B+Cd+same element as detector, when combined with a parallel monitor, make possible accurate studies with defined neutron energies.

Methods for production and detection of neutron beams with sharply defined and continuously variable energy are essential. In the low energy region, the electrical velocity selector of Alvarez is considerably more satisfactory than the mechanical selector, and should be applicable from $\sim$0 to $\sim$10 ev at least. The neutron crystal spectrometer now further developed by Thiessen offers possibilities, especially in the region less than 1/20 ev.

The wave-length of thermal neutrons of 1/30 ev is 1.6A, which is comparable with atomic spacings in solids. Interference phenomena thus play an important role in neutron interaction with solids, somewhat similar to x-rays, as shown by recent work. The need for more accurate investigation of neutron interaction as a function of energy is thus emphasized, both from the standpoint of nuclear research and for the application of neutrons to solid state studies.

General III

Protection of Workers from Injurious Effects of Radiation

Chairman: DR. G. FAILLA, *Memorial Hospital, New York, New York*

52. Biological Damage and Precautionary Tests. STAFFORD L. WARREN, *Department of Radiology, University of Rochester, School of Medicine and Dentistry, Rochester, New York.*

The exposure hazards to those working with cyclotrons are not well known, but the potential hazards are increasing since equipment is becoming more and more powerful. So far very little known damage to personnel has been observed partly because of the precautions which were taken by the early workers and partly because of the relative weakness of the output of the present cyclotrons. Immediate reactions from direct, accidental exposures to the cyclotron beam have been confined to the skin, and to date have not been serious. They resemble a severe reaction to ultraviolet radiation in many respects, except for the slowly receding superficial edema and erythema, and the minimum of exfoliation. There is no evidence yet available as to their possible sequelae.

Exposure to gamma- and beta-radiation bears the same hazards as that to workers who handle radium and x-rays, and is well known to workers in this field. Long-time exposure of the body to relatively small amounts of gamma-radiation has cumulative effects which are probably most marked upon the blood forming elements of the bone marrow. Neutrons and the protons arising from them may cause damage in any portion of the body. If we speculate that their cumulative and possibly harmful effects will be found in those tissues of the body most susceptible to x-rays when the whole body is exposed, then the blood forming organs will be probably among the first to suffer. Accidental localizations may of course alter the situation.

Hence routine blood examinations (white blood cell count and hemoglobin as a minmum) should be done, certainly every month on all those working with a cyclotron to obviate the possibility of accidental and unpredictable exposure, even though every effort is made to design the apparatus in such a way as to prevent this. If any fall in

the white blood count is noted, that person should be removed from all exposure and a thorough physical examination and complete blood study made to determine the cause of the leukopenia. Frequent blood examinations should then be made and the individual should not return to work until he is normal. Many intercurrent infections of very mild character may produce the same result so that considerable clinical judgment is necessary at times in evaluating the status of the individuals. Vacations should be adequate and should total at least one month in the year. A senior physician should be made responsible for the supervision of the medical status of all of the personnel. Since most cyclotron laboratories are connected with universities, such arrangements can often be simply made with physicians having experience with radiation effects in allied or university hospitals. It might not be out of order to suggest periodic tests of the working area with a Geiger counter-ionization chamber to detect unsuspected gamma-radiation, and also to stipulate that the personnel wear the common dental film, one-half shielded on both sides by 2 mm lead. This should be examined every week. Enough exposure to darken the film and show an image of the shield edge within a week probably represents a hazardous amount of radiation exposure. A condenser type of ionization chamber (fountain-pen size) should also be worn when "beam" adjustments are being made.

In speculating as to the probably acute and chronic damage that may be brought about by these radiations and particles, it is probably wise, and certainly safer, to predict a 10–20 times greater hazard than experience has shown to be present from equivalent quantities of other radiations.

53. Genetic Changes. M. DEMEREC, *Carnegie Institution of Washington, Cold Spring Harbor, New York.*

Genetic changes are usually taken to mean changes which are transmitted from parents to their offspring. In one sense this is correct, since only changes transmitted to the offspring are able to persist through generations. However, since as a rule every cell of an organism possesses identical genetic material, the same genetic changes may occur both in germ cells which transmit these changes to the offspring and in somatic cells which do not. Since germ-cells and somatic cells have identical genetic constitution both are used in the studies of genetic changes.

In a very few branches of biologic science, the fundamental principles are as applicable to all living organisms as they are in genetics. It is a well established fact that fundamental principles discovered on plants hold for animals and vice versa. Man is no exception to that rule.

Hereditary material in the cells is present as differentiated regions called genes located on thread-like structures called chromosomes. The number of genes in every organism is large, it is estimated that the vinegar fly, Drosophila, has between 3000 and 5000 different genes which are present in every cell of the body. Many of them play an exceedingly important role in life processes and if any of these are missing, the organism, or even individual cells are not able to persist. Every chromosome has a differentiated region called centromere which is essential in order that at the division of a cell a chromosome may be passed to the daughter cells. If a chromosome breaks, only the segment with the centromere will be transmitted while the other segment is soon lost.

With this general background in mind, the effect of radiation on heredity may now be considered. It is known that irradiation in the regions about 0.01A to 2.4A and about 2300A to 3000A is able to produce changes in genes as well as breaks in chromosomes. It is well known that a great majority of gene changes are either lethal or injurious to the organism. Breaks in chromosomes may result in either losses of segments, or if several breaks are induced in the same cell, broken points may fuse and thus a reshuffling between chromosome segments may result. In the organisms like Drosophila losses of segments are almost invariably lethal and reshufflings give rise to aberrations some of which are lethal while others behave in a manner similar to that produced by changes in genes.

As an illustration of the genetic effect of irradiation the results of a series of experiments with Drosophila may be used. If males are treated with 5000 roentgens, the sperm in the testes is irradiated. Such males copulate readily and are able to impregnate females. The sperm so transferred is alive and functional, it fertilizes the eggs. However, about 90 percent of individuals arising from such fertilizations die before reaching adult stage, most of them in the early embryo, but some in later stages of development. Of the individuals which live to adult stage about 40 percent carry chromosomal rearrangements and about 12 percent lethal changes. It seems very likely that an exceedingly small number of them escape some detrimental hereditary change.

Experimental evidence indicates that there is no threshold for genetic changes. They are proportional to the dosage used. At very low dosages changes are induced but with a very low frequency. J. G. Carlson has shown that as low a dose as 7.8 roentgens produces 0.34 percent of breaks per treated chromosomes in the neuroblast cells of grasshoppers.

It is a well-substantiated fact that there is no recovery in hereditary changes, neither genic nor chromosomal. Therefore the effect of irradiation is cumulative. This holds true for individual cells, but not for a dividing tissue. The rate of cell division is slowed down in affected cells and an appreciable number of them is eliminated from the tissue. Therefore the proportion of affected cells in dividing tissue will decrease with the length of time which elapses after the treatment. For example, if a Drosophila male is treated with 3000 roentgens, the sperm which was mature at the time of treatment carries about 60 percent of dominant lethals, while the sperm which develops later carries only about 10 percent of dominant lethals. In this case, the larger portion of lethal changes were eliminated during two cell divisions which occurred between irradiation and the maturity of the sperm.

Geneticists are interested in the mechanism responsible for genetic changes and have accumulated a large body of data on the dosage frequency relationship, wave-length

dependence, and biological behavior. However, considering the tolerance dose for protective purposes in addition to these data the selective effect of cell divisions plays an important role. The data on that effect are not yet available.

54. Protective Measures Against X- and γ-Rays. LAURISTON S. TAYLOR, *National Bureau of Standards, Washington, D. C.*

Protection against danger from x- or γ-rays may be had for the asking, the degree of complication and expense depending upon whether protection from direct or secondary radiation is sought. For protection against direct radiation it is desirable to place the barrier as close as possible to the source, where in most cases the increase in thickness of barrier is more than offset by its decrease in total mass. In experimental work canalization of the direct radiation is usually possible. Observers by remaining away from the beam may then be very economically protected by various means. A wide variety of protective materials may be used, depending upon circumstances,—these include lead, lead shot, concrete, mercury, copper-tungsten alloys, barium compounds. Illustrations of the use of these will be given.

55. Protection from Neutron Rays and Other Products of Nuclear Transformation. PAUL C. AEBERSOLD,* *William H. Crocker Radiation Laboratory, Physics Department, University of California, Berkeley, California.*

So rapid has been the expansion both in the production and in the uses of nuclear transformation products, particularly neutrons and induced radioactive substances, that it is timely and highly desirable to call attention to the protection necessary to avoid injurious effects upon those exposed to the radiations involved. To physicists accustomed to very delicate methods of detecting nuclear products the realization comes slowly that quantities of radiations and radioactive substances are produced by present bombarding apparatus that necessitate serious consideration of the problem of protection. Inasmuch as the nature and penetration of some of the radiations are different from those dealt with previously, it is necessary to proceed with caution in arriving at rules of safe practice. Therefore, without claim to specifying a set of protection rules, as are now possible for x-ray apparatus and radium, this paper proposes to give only some of the considerations used in arriving at protective measures for the Berkeley cyclotrons.

The average daily tolerance limit of exposure adopted for the gamma-rays encountered from cyclotron bombardments and radio-elements is the same as that adopted by radiologists for x-rays and radium, namely 0.1 r/day. Should another value seem desirable the following values would be changed accordingly. For fast neutrons a tolerance dose is assumed that is biologically equivalent to 0.1 r of x-rays. This equivalence was originally determined by experiments on animals and other organisms. Because of the application of neutrons in cancer therapy, equivalence can now be based on reactions of human tissues to neutrons.

An arbitrary unit, called the "n," has been found useful and expedient in measuring neutron dosage. It is the exposure of neutrons that will cause in the Victoreen x-ray r-meter chamber (100 r, 0.5 cc size) the same reading as an exposure of 1 r of x-rays. A marked human skin reaction corresponding roughly to that caused by 1000 r of x-rays is produced by 200 n of neutrons. Taking, as for x-rays, the daily tolerance to be 10^{-4} of the single dose for epithelial reactions (such reactions being used by radiologists as guides in avoiding permanent tissue damage) the value for neutrons would be 0.02 n/day. Since on some organisms 1 n was found as effective as 10 r, the tolerance we have adopted is 0.01 n/day. This allows for the possibility that the sensitivity of some tissue in the body with respect to that of skin may be twice as great for neutrons as for x-rays. Although there is a possibility that the recovery of normal human tissues from repeated minute doses of neutrons is much less than that for x-rays, experience with neutron therapy indicates no large factor need be considered on this score. In actual practice, the average daily exposure of workers in the laboratory falls below the above limit.

Table I gives approximations of the intensities involved and the distances or water shielding necessary for protection. The n intensity per curie source strength is an upper limit based both on calculations and available data. Measurements show that the 37-inch and 60-inch cyclotrons operate at curie strengths of more than 10^5 and 10^6, respectively. The safe working distances are merely calculated by inverse square decrease and take no account of absorption, scattering, and secondary radiation. Rigorous calculations of the penetration of neutrons through water shields are complicated, but a sufficient approximation can be made assuming exponential absorption. Values are given which assume that an appreciable fraction of the neutrons have mean free paths as large as 15 and 20 cm. Using neutron indicators in water shields around the 60-inch cyclotron, $\lambda = 12$ cm was found applicable for neutrons from 16-Mev deuterons on beryllium. However, the thicker shields calculated on the basis of $\lambda = 15$ cm are advisable because of secondary radiation created at depths in the shields.

The following things are recommended for shielding a 60-inch cyclotron: (1) the emergent ion beam directed

TABLE I

CURIE STRENGTH OF SOURCE	N PER 8-HR DAY AT 10 METERS	TOLERANCE WORKING DISTANCE IN METERS NO SHIELDING	THICKNESS OF WATER TANKS IN CENTIMETERS FOR TOLERANCE AT 10 METERS	
			$e^{-r/15}$	$e^{-r/20}$
1	10^{-4}	1	0	0
10	10^{-3}	3.2	0	0
10^2	10^{-2}	10	0	0
10^3	10^{-1}	32	34.5	46
10^4	1	10^2	69	92
10^5 (37-inch cyclotron)	10	320	103.5	138
10^6 (60-inch cyclotron)	10^2	10^3	138	184
10^7	10^3	3200	172.5	230
10^8	10^4	10^4	207	276

away from working quarters, (2) completely surrounding walls of water at least five feet thick, (3) a roof and floor equivalent to at least three feet of water, (4) a minimum of openings through the shielding, (5) additional shielding provided wherever possible between the magnet coils directly around the target and vacuum chamber, and (6) a concrete-walled control room over ten meters away.

* Fellow of the Finney-Howell Research Foundation.

56. Protective Requirements for Shipping Radioactive Substances. L. F. CURTISS, Physicist, *National Bureau of Standards, Washington, D. C.*

During the last five years the shipment of radioactive substances has been given considerable attention. This was brought about by the discovery by the Post Office Department that photographic films were fogged in transit by radium preparations shipped in close proximity. An order excluding radium and similar radioactive substances from the mails followed.

The express companies were willing to continue to handle shipments of radium if methods could be worked out which would preclude damage to films. Conditions under which these companies handle shipments are more flexible than those under which the mails are handled and regulations have been drawn up by the express companies which are the result of tests at a number of laboratories and conferences between the manufacturers of photographic films and the principal shippers of radium.

The factors entering into the fogging of films are: (1) the strength of the radioactive preparation; (2) the time that the film is exposed to the preparation; (3) the distance between the radioactive sample and the film; (4) the thickness of lead screening on the radium; (5) the sensitivity of the film.

In the practical solution of the problem, the distances are determined from the conditions existing in the average express car. The maximum separation of packages containing films and radium in such cars is approximately 20 feet. Therefore, the table used is based on x-ray films, which are most sensitive to radium, placed at 20 feet from all packages of radium. This table shows the relation between the amount of radium, the thickness of lead and the permissible number of hours in transit. This is shown in Table I.* In order to make this arrangement workable it is necessary that all packages of photographic films and of radium be clearly marked as to contents. In addition, a label stating the amount of radium contained in a package and the thickness of lead surrounding it is required by the express companies.

Although this table includes shipments up to 600 mg of radium, the express companies accept shipments only up to 100 mg without previous consultation with the local agent. This is to permit special arrangements to be made in handling the larger shipments so that they may be carried in cars not containing photographic films.

The lead screening required by these regulations is much greater than was required formerly. Some examples of the way in which this problem has been solved by individual shippers will be discussed.

Allowable Time of Transit for Radium (Table 1 of Abstract No. 56)

QUANTITY OF RADIUM: Milligrams	THICKNESS OF LEAD—INCHES $\frac{1}{4}$	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	$2\frac{1}{2}$	3	$3\frac{1}{2}$	4
	Allowable hours in transit								
Under 15 mg.	40	60	110						
15 mg and under 25	20	30	55	110					
25 mg and under 35	14	20	36	73	146				
35 mg and under 45	10	15	28	55	110				
45 mg and under 55		12	22	44	88	170			
55 mg and under 65		10	18	36	73	142			
65 mg and under 75			16	31	63	122			
75 mg and under 85			14	27	55	106			
85 mg and under 95			12	24	48	93			
95 mg and under 100 incl.			11	22	44	85	170		
200 mg				11	22	43	86	172	
300 mg					14	28	56	112	
400 mg					11	22	44	88	172
500 mg					8	17	34	68	136
600 mg						14	28	56	112
Minimum weights of lead, pounds	$\frac{1}{4}$	$\frac{3}{4}$	$3\frac{1}{4}$	$9\frac{1}{4}$	$9\frac{1}{4}$	36	$58\frac{1}{2}$		

General IV

*Contributed Papers**

Chairman: DR. ROBERT J. VAN DE GRAAFF, *Massachusetts Institute of Technology*

91. The Significance of the Hit Theory of Radiobiological Actions. UNO FANO, *Carnegie Institution of Washington, Cold Spring Harbor, New York.*

Numerous experimental radiobiologists are still in doubt as to whether their results agree with the so-called "hit theory" and especially whether they yield any definite evidence supporting it. An attempt has been carried out to examine critically the logical structure of the hit theory and its bearing on the known experimental facts.

Simple, quantitative—perhaps unduly schematized—biological reactions have been taken as indicators of the radiation effects under physically controlled conditions; dose-action curves and their dependence upon the characteristics of the irradiation have thus been studied. The hit theory offers a simple interpretation of various results of these experiments. It seems, however, that such results do not necessarily require the hypothesis of the theory itself (the evidence is more convincing in the "single hit" case than in other cases). It is difficult to obtain any better evidence through further experiments of the same type. For instance the behavior of dose-action curves is critically affected by the theoretical assumptions only in the hardly accessible ranges corresponding to exceedingly low or exceedingly high dose.

Further evidence should be obtained through experiments involving more detailed observations of the biological reactions. Results available at present show that the complication of some phenomena considerably exceeds that of their previous interpretations on the basis of the hit theory.

Some theoretical considerations, which might stimulate further experiments, can be put in a general form so that they are still valid even if the usual restrictive assumptions of the hit theory are rejected.

92. The Effect of Fast Neutrons on the Chromosomes of Tradescantia. NORMAN GILES, *Biological Laboratories, Harvard University, Cambridge, Massachusetts.*

Fast neutrons were produced by bombarding a beryllium target with 11-Mev deuterons in the Harvard cyclotron and their effects on the chromosomes of Tradescantia during microspore development have been investigated and compared with the effect of x-rays. Qualitatively the results are the same as those produced by x-ray treatment, and consist of chromosome breakage and the refusion of broken ends. Quantitatively, however, neutrons appear to differ considerably from x-rays in their effect on chromosomes. For equal total doses in terms of ionization as measured with a Bakelite Victoreen ionization chamber neutrons are from 16 to 17 times as effective as x-rays in producing chromatid dicentrics—an aberration type known to result from a single x-ray hit. Also, exchange break aberrations, producing chromatid and chromosome rings and dicentrics, are found to show an approximately linear relationship to dosage instead of the exponential relation found with x-rays. An attempt is made to explain these differences between neutrons and x-rays in terms of the great difference in the types of ionization paths which these two radiations produce in tissue.

93. Magnetic and Metallurgical Studies with the Aid of Neutron Phenomena. OTTO HALPERN, *Department of Physics, New York University, University Heights, New York.*

The magnetic moment of the neutron gives rise to a large number of additional scattering phenomena occurring during its passage through magnetic material. Theories have been developed which permit to obtain information from neutron experiments, on the magnetic, crystalline and elastic structure of the materials used. This new evidence refers among other things to the domain structure of ferromagnets, to the dependence of the domains on the crystalline state of the material and the external or internal stresses, and to the influence of external magnetic fields on the size of the domains. For paramagnetic materials information concerning the inter-atomic magnetic coupling can also be gained. Even for nonmagnetic materials, experiments with neutrons sometimes lead to results, concerning the crystalline arrangement of alloys, which cannot be gained from x-ray studies. Examples are discussed.

94. Preparation of Radio-Arsenic for Biological and Chemical Experiments. JOHN W. IRVINE, JR., *Department of Physics, Massachusetts Institute of Technology, Cambridge, Massachusetts.*

Radio-arsenic, $_{33}As^{74}$ with a 17-day half-life can be produced by a *d-n* reaction on germanium.[1] The arsenic so formed is in a mixture of germanium, copper, tin, lead, and minor impurities. To free it from these impurities and reduce the element to a form in which it can be used, the following procedure is used. The target is dissolved in aqua regia, some carrier arsenic added, and the solution evaporated to dryness. This removes the excess HNO_3 and most of the germanium. Concentrated HCl and a small amount (5 cc) concentrated HBr are added and distilled into a chilled receiver. The HBr reduces the As^{+5} to As^{+3} which passes over with the HCl and Br_2 as $AsCl_3$. This distillation is repeated after the addition of more acid to the residue. To the combined distillates an excess of $NH_4H_2PO_2$ is added, and the solution warmed to 90°C for five minutes. Metallic arsenic precipitates, and is filtered out through a porcelain micro-filter crucible. From this point the arsenic can be converted to any form suitable

* Proofs of the abstracts printed in this section were not read by the authors.

for its use. In our work it is oxidized to As_2O_3 and dissolved in $KHCO_3$ to make Fowler's solution. Yields of 65–75 percent are obtained by this method when 1 to 10 mg of carrier are used. By carrying out the distillation in a stream of hydrogen chloride, the yield can be raised to 95–100 percent.

[1] Sagane, Kojima and Ikawa, Phys. Rev. **54**, 149 (1938).

95. Effects of Inhaled Radon on Mice. MELVIN L. JACKSON, *Massachusetts Institute of Technology, Cambridge, Massachusetts.*

A system consisting of an animal house with provision for a continuous supply of radon-laden air has been used in subjecting 60 male mice to an atmosphere of *ca.* 2×10^{-6} Curie per liter since July 2, 1940. The continuous exposure is interrupted only for removing dead animals or at approximately weekly intervals when 12 blood specimens are taken, weights recorded, and food and water replenished. The average blood counts with their probable errors are shown in the table. Erythrocytes are given in $10^6/mm^3$, total leukocytes in $10^3/mm^3$. See Table I.

TABLE I.

Days	0	6	12	18	25	33	41	52	62	71
Erythrocytes	9.4	9.4	9.7	9.6	10.4	11.1	10.9	11.1	11.7	10.4
Probable Error	±0.2	±0.2	±0.3	±1.0	±0.2	±1.1	±0.2	±0.2	±0.2	±0.2
Leukocytes	10.1	12.8	12.3	9.1	9.7	9.2	8.5	7.6	14.8	9.6
Probable Error	±0.8	±1.1	±1.1	±0.8	±1.0	±0.8	±1.0	±0.7	±1.0	±1.1

All of the mice were between two and four months old at the beginning of the experiment. At the end of 6 weeks, of 8 deaths none could be attributed to the effects of radon inhalation, although pathological changes similar to those due to x-rays were noted. Two pregnant mice gave birth to 11 offspring 12 hours after being placed in the animal house. These mice are being raised in the radon atmosphere. These inhalation experiments, conducted by a group including Professor R. D. Evans of Massachusetts Institute of Technology and Dr. J. C. Aub and Dr. Eugene Wiege of the Collis P. Huntington Memorial Hospital, are still in progress.

96. The Effect of 200-kv X-Radiation on the Extraneous Coats of Arbacia Eggs. M. J. KOPAC, *New York University and the Marine Biological Laboratory, Woods Hole, Massachusetts.*

Mature sea-urchin eggs possess several extraneous coats, including an outer jelly layer and a vitelline membrane which covers the protoplasmic surface layer. On sperm or chemical activation, the vitelline membrane separates from the surface layer, elevates, stiffens, and becomes the fertilization membrane. A few minutes later, a hyaline layer is secreted by the egg and this coating lies on the protoplasmic surface layer. The latter coating is of interest since it eventually becomes an intercellular cement which binds together the blastomeres of the developing larva.

Evans[1] has shown that high voltage x-radiation greatly accelerates the dispersal of the jelly layer. The vitelline membrane is also affected by similar radiation. The action of x-radiation on the vitelline membrane can be traced by measuring the coalescency of the eggs with oil drops.[2] This method permits the evaluation of the tangential rigidity of the protoplasmic surface layer as well as extraneous coats.

Coalescency determinations on eggs were made at various times after irradiation. Dosages of 1000r produced no change during the first hour, but at 6 hours the tangential rigidity dropped to 0.7, and to 0.17, 24 hours later. Dosages of 10,000r caused a decrease in tangential rigidity to 0.25 of the control value during the first hour, to 0.14 at 6 and 24 hours. These two dosages did not produce any appreciable stickiness of the vitelline membranes. Dosages of 50,000r caused a drop in tangential rigidity to 0.67 during the first hour in about 50 percent of the eggs, with no significant change at 6 hours and a drop of 0.1 after 24 hours. These eggs showed no visible membranes but all exhibited a pronounced stickiness to glass and to oil drops. Oil drops pulled away from the egg's surface, usually carried with them a small pinched-off portion of the egg, resembling in this respect the behavior of unfertilized eggs immersed in 0.34*M* $CaCl_2$ solution. About 50 percent of the eggs irradiated with 50,000r developed tight-fitting fertilization membranes and a fully formed hyaline layer. The perivitelline space was essentially non-existent. In all cases, including nonradiated controls, the vitelline membrane is slowly dissipated and this shown by the low tangential rigidities as measured 24 hours after irradiation.

[1] Evans, Biol. Bull., in press.
[2] Kopac, Cold Spring Harbor Symposia, 1940, in press.

97. Radioactive Comparison of Meteoritic and Terrestrial Potassium. WILLIAM M. LEADERS, *Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts.*

The relative abundance of the beta-active isotope K^{40} has been determined by radioactive measurements in potassium chloride obtained from the Pultusk meteorite and the earth. The results indicate no difference within the limits of the statistical error.

Thus, according to the basic assumption for age determination; namely, all elements have the same isotopic abundance ratios at the time of formation, there is no difference in age between the Pultusk meteorite and the earth within the limits of statistical error.

The potassium recovered from the meteorite corresponds to 0.28 percent K_2O. The purity of the potassium chloride, obtained with the aid of the perchloric acid alcohol method is not less than 99.25 percent with the major impurity being calcium and not more than 0.15 percent rubidium present. These percentages are based on spectroscopic analyses. The terrestrial potassium chloride was not less than 99.94 percent pure and contained no detectable rubidium.

The samples of potassium chloride were mounted as a fine powder. This technique greatly facilitates the determination and makes it possible to obtain around eight weight *versus* activity measurements per day. This method could advantageously be employed, therefore, for rapidly determining the activity of weakly active substances obtainable in weighable quantities.

The numerical comparisons of the activity of the two samples of potassium were obtained by extrapolating the experimentally obtained specific activity *versus* weight curves to the point of zero sample weight.

98. The Interchange of Uncombined Oxalate Ions with the Oxalate of Several Complex Oxalate Ions. F. A. LONG, *Department of Chemistry, Cornell University, Ithaca, New York.*

Radioactive potassium oxalate has been synthesized from radio-carbon (20 min. half-life). This radioactive oxalate has been used to study the interchange of uncombined oxalate ions with the oxalate present in complex ions of the type $M(C_2O_4)_3^{\equiv}$. The interchange has been studied for ferri-trioxalato, aluminum-trioxalato and cobalti-trioxalato ions. The cobalt complex shows no interchange and thus is similar to the previously studied chromium complex ion. The other two complex ions, however, show complete and rapid interchange of their oxalates.

These experimental results can be correlated with the expected bond types for the four complex ions. The results have direct bearing on the problem of the reported optical activity of salts of these complex ions. The conclusion is that the rapid interchange makes optical activity very unlikely for the ferric and aluminum compounds although it does not suffice to exclude entirely such optical activity.

99. The Use of Radioactive Isotopes in Studies of the Permeability of the Human Erythrocyte. ALEXANDER W. WINKLER, ANNA J. EISENMAN AND PAUL K. SMITH, *Department of Internal Medicine and the Laboratory of Pharmacology, Yale University School of Medicine, New Haven, Connecticut.*

Studies recently completed in these laboratories have made use of the radioactive salts of sodium, potassium and phosphorus to determine whether these elements as they exist in the human red cell are in equilibrium with the same elements in the serum.

It has been shown that no equilibrium develops *in vitro* between the intracellular and extracellular potassium either at body temperature or at 7°. Some transfer of sodium did occur, but the degree of radio-sodium penetration was so small that it could not be shown whether an equilibrium existed. Phosphate entered rapidly at body temperature but not at 7°. At 38° there was active synthesis and breakdown of organic phosphorus compounds. This was interpreted as evidence that the penetration of phosphates into the red cell depends upon an enzymatic process.

To determine whether the chloride in the cells is in equilibrium with the chloride of the serum, lithium chloride was used. Human blood was defibrinated and centrifuged, the dried salt dissolved in the supernatant serum and the cells recombined with the serum. The samples were placed for definite periods of time in large tonometers and rotated slowly in a water bath at 38°. Hematocrits were determined with Daland tubes. Part of each specimen was set aside for whole blood analyses, the rest being centrifuged to obtain the serum for analysis.

Radioactivity was determined by the use of a Geiger-Müller counter tube that dipped into the solution to be analyzed. The whole blood was hemolyzed with saponin before counting. The exact time of each count was noted to permit correction for the rapid decay of Cl^{38}. Chloride in the whole blood and serum was determined chemically. The concentrations of chloride and radio-chloride in the cells were calculated from the hematocrits and the whole blood and serum determinations. Under these circumstances equilibrium between chloride in and out of the cells exists if the ratio of radioactivity to chloride in the cells is equal to the ratio of radioactivity to chloride in the serum.

Our experiments indicate that when radio-chloride is added to human blood *in vitro* at 38° an equilibrium is quickly established between the chloride of cells and of serum. Equilibrium was usually complete in one hour and in some cases in fifteen minutes. All radioactive samples were prepared by Dr. Ernest Pollard of the Sloane Physics Laboratory, Yale University.

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Letter to the Editor

Anti-Reflection Films on Glass Surfaces

A. F. TURNER
Bausch and Lomb Optical Company, Rochester, New York
February 25, 1941

THERE recently appeared in *Nature*,[1] a communication from J. W. French in which certain statements are made regarding anti-reflection films that would seem to require comment. The author refers to the conditions which the films must satisfy in order to produce by interference a zero reflected beam, *viz.*, that "(1) equal portions of the light are reflected back from the outer and inner surfaces of the film, (2) the phases of these portions are such that they interfere with and neutralize one another so far as visual reflection is concerned, (3) the cryolite film must have a definite thickness."

In passing it may be remarked that condition (1) is satisfied for the s component when

$$\frac{n_2^2}{n_1 n_3}=\frac{\cos a_1 \cos a_3}{\cos^2 a_2}=\cos (a_1-a_3) \qquad (1)$$

and for the p component when

$$\frac{n_2^2}{n_1 n_3}=\frac{\cos^2 a_2}{\cos a_1 \cos a_3}, \qquad (2)$$

where n_1, n_2, n_3, are the indices of refraction of the outer medium (e.g., air), the film and the glass, respectively, and a_1, a_2, a_3, are the angles between a normal to the surfaces and the rays in the three media, respectively. These relations, derived from the Fresnel formulae, have been published in a different form by K. B. Blodgett.[2] Conditions (2) and (3) are satisfied when the geometrical film thickness d is given by

$$2n_2 d \cos a_2=\lambda_{\min}/2. \qquad (3)$$

For normal incidence, the above expressions simplify to the more familiar conditions that (1) the index of the film be equal to the square root of that of the glass, and (2) the optical thickness of the film be a quarter wave-length.[3]

Dr. French continues, "Such a theory might explain the reduced reflection on the basis of interference. It does not explain the increased transmission, the factor of real importance." These statements are difficult to understand in view of the complementary character of interference phenomena in reflection and transmission as, for example, Newton's rings. The reason for the increased transmission of a glass surface with a quarter-wave film will be clear if one sketches a diagram of the transmitted rays, including those arising from multiple reflections within the film. Since the latter traverse the quarter-wave film an even number of times and in addition suffer a 180° change of phase at the film-glass innerface, they are integral multiples of a whole wave out of phase with the direct transmitted ray. Accordingly, they reinforce it by interference. The additional transmitted energy is obtained at the expense of a weakened reflection, and it is scarcely necessary to add that spectrophotometric measurements of filmed plates always verify this.

Further it is stated: "In practice, so far as transmission is concerned, precise control of the thickness is not necessary. It is determined only by mechanical considerations." We cannot concur. It has been our experience that for maximum visual white light transmission the film thickness should be carefully controlled to ±10 percent of the correct thickness for maximum transmission in the green. This is in accord with calculations. To determine the white light transmission of a filmed surface as it would be measured with a visual photometer one may compute Y of the I.C.I. tristimulus system, since Y gives the brightness directly. As an example the computed values of Y are given in Table I for a beam of white light transmitted normally

TABLE I. *Computed visual transmission of glass, $n_3=1.57$, with $\lambda_{\min}/4$ film, $n_2=1.34$. (Y Values for Illuminant C.)*

$\lambda_{\min}$	1 SURFACE	2 SURFACES	4 SURFACES	8 SURFACES
400 mu	0.9870	0.9742	0.9491	0.9008
510	.9943	.9887	.9775	.9555
550	.9950	.9899	.9799	.9602
590	.9945	.9889	.9779	.9564
700	.9875	.9753	.9512	.9051
No Film	.9508	.9041	.8173	.6680

through various numbers of surfaces of glass of index $n_3=1.57$ filmed with a material of index $n_2=1.34$. The wave-length $\lambda_{\min}$ at which the film is optically just a quarter-wave thick has been located at five different positions in the spectrum. No account has been taken of multiple reflections between the filmed surfaces so the results are applicable, for instance, to the direct image transmitted by a series of lens surfaces, as in a camera objective. The energy transmission of an individual filmed surface is[4]

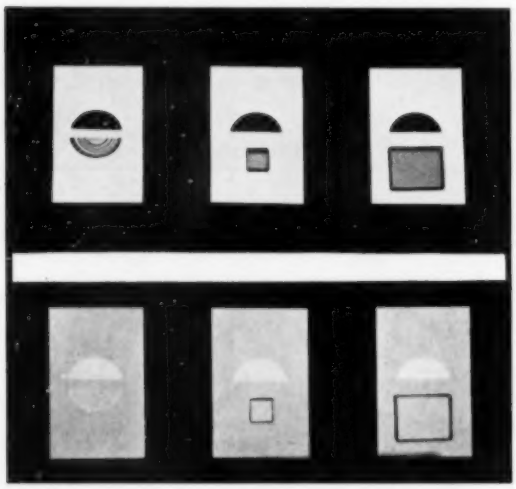
$$I_d=(1-r_1^2)(1-r_2^2)/(1+2r_1 r_2 \cos\theta+r_1^2 r_2^2), \qquad (4)$$

where r_1 and r_2 are the reflected Fresnel amplitudes from the air-film and the film-glass surfaces and θ is the phase difference between successive transmitted beams, arising from multiple reflections within the film, disregarding, however, any change of phase by reflection at the film surfaces. For normal incidence as assumed here $\theta=\pi\lambda_{\min}/\lambda$.

The table indicates that the visual white light transmission is affected only by a few tenths percent, even with eight surfaces, for a variation of the quarter-wave position from 510 mu to 590 mu. Displacing it further, however, causes a rather rapid decrease in transmission. Thus for eight surfaces the transmission drops by 6 percent when the quarter-wave position reaches the extremes of the visible spectrum. It should be pointed out that for a nonselective receiver, in contrast to the eye, the change in observed transmission over the same wave-length range, 400 mu–700 mu, will be still greater than the above figures for a given displacement of $\lambda_{\min}$. Apparently an accurate control of film thickness is imperative.

The *Nature* communication presents a calculation of the increase in transmission expected from filming both surfaces of a glass plate of index 1.65 with a film material of index 1.35. The computation is done as indicated in

Strong,[5] the loss of light being assumed to be the sum of the Fresnel reflectances of the air-film surface and the film-glass surfaces. Such a procedure is applicable to a thick surface layer where interference is neglected, and amounts to using only the numerator of Eq. (4). For the indices of refraction given, the transmission increase for thick layers is 6 percent. This value Dr. French states "agrees with experience." If, however, we have a quarter-wave interference film of correct thickness for optimum visual work the calculated increase in transmission should be about 12 percent and this is substantiated by measurements on a



(a) (b) (c)

FIG. 1. Illustrating the difference in effectiveness of thick and "thin" surface layers. Photographs of three glass plates, $n_2 = 1.66$, with quarter-wave films (semicircular) and thick layers of (a) sodium aluminum fluoride, (b) LiF, (c) CaF_2. Lower row taken by transmission; upper row by reflection, background black.

filmed plate shown in the photographs, Fig. 1*a*. To demonstrate the difference in reflection losses from thick and thin (quarter-wave) surface layers three plates of index $n_2 = 1.66$

TABLE II. *Observed increase in transmission of glass plates, $n_2 = 1.66$, of Fig. 1.*

	Sodium Aluminum Fluoride	LiF	CaF_2
Thick Layers	1.07*	1.05	1.03
Quarter-Wave Films	1.11	1.11	1.11

* Computed.

were provided with quarter-wave films of sodium aluminum fluoride ($n_2 = 1.34$), LiF ($n_2 = 1.39$) and CaF_2 ($n_2 = 1.43$). These were evaporated through a semicircular mask on both sides of the plates. For comparison, thick (2 or 3 mm) plates of LiF and CaF_2 were cemented in register to each side near the respective evaporated films. Since clear thick plates of sodium aluminum fluoride were not obtainable, a mound of this material was evaporated on one side through the semicircular mask near the quarter-wave film of the same material. The mound is optically a quarter-wave thick at the periphery and increases to a thickness of two wave-lengths at the center. Here it may almost be termed a "thick" film for the effective wave-length sensitivity range of the photographic emulsion-illuminant combination used, since the interference rings have become indistinct. Visual white light measurements of the ratio of transmissions of the glass plates with and without the surface layers were as given in Table II. These measured ratios agree well with computed values.

[1] J. W. French, Nature **146**, 687 (1940).
[2] K. B. Blodgett, Phys. Rev. **57**, 921 (1940).
[3] See, for instance, U. S. Patent 2,207,656.
[4] Wien-Harms, *Handbuch der Experimental Physik* (Leipzig, 1928), Vol. 18, p. 234.
[5] J. Strong, J. Opt. Soc. Am. **26**, 73 (1936).

New Books

Phenomena at the Temperature of Liquid Helium

By E. F. Burton, H. Grayson Smith and J. O. Wilhelm. Pp. 362+xi, Figs. 104, $15\frac{1}{2} \times 23\frac{1}{2}$ cm. American Chemical Society Monograph Series No. 83, Reinhold Publishing Corporation, New York, 1940. Price $6.00.

Any satisfactory discussion of the behavior of matter at low temperatures must consist to a large extent of the comparison of this behavior with the more familiar behavior at ordinary temperatures. The authors have realized this, and having selected as their subject matter those phenomena which are most interesting or significant at the temperature of liquid helium, they have treated these phenomena fully, without limitation on the temperature region involved. For this reason the book is equally valuable to all low temperature workers, whether they have liquid helium available or must be content with liquid hydrogen or liquid air.

The book may be divided into two parts. The first part, Chapters 1 to 5, is mostly nonmathematical and entirely nonquantal. Chapter 3 on temperature measurement is more complete than one might expect in a book of this type, but at some points is lacking in clarity. Chapters 4 and 5 deal with liquid and solid helium and with superconductivity. In general, the approach here is historical and experimental, and the parade of experiments may well prove to be the most interesting part of the book to one with only a casual acquaintance with the low temperature field.

The professional low temperature scientist, however, will probably prefer the second part of the book (Chapters 6 to 11). It is in this section that one finds specific heats, order-disorder transitions, para- dia- and ferromagnetism, adiabatic demagnetization, electrical and thermal resistance, thermodynamics of superconducting transitions, London's equations for superconductors, helium II and Bose-Einstein condensation, and many other topics methodically discussed. The general method of treatment is to

develop the theory of a given topic in condensed form, compare it with experiment, then pass to a related topic. The question of how far to carry the process of abbreviating a theoretical derivation is one of individual judgment. It seems to the reviewer that the authors have solved this problem rather successfully, and have managed to include a maximum of useful information without making the book over long. Some errors can be found, but not so many as to detract seriously from the worth of the book, which should prove to be of great value to all those working in the low temperature field.

The diagrams are well drawn and illuminating, and the references, of which there are an average of 60 per chapter, furnish a valuable key to the literature. The author and subject indexes are adequate.

HAROLD J. HOGE
National Bureau of Standards

Electromagnetic Theory

BY J. A. STRATTON. Pp. 615+xv, Figs. 116, $15\frac{1}{2}\times23\frac{1}{2}$ cm. McGraw-Hill Book Company, New York, 1941. Price $6.00.

This is a most excellent book. In it the electromagnetic theory is developed deductively from Maxwell's equations, without the common effort to produce a spurious simplicity by the omission of the powerful general methods of treatment and the practically useful problems. It is no book for a nonmathematical beginner, but for a person well grounded in mathematical technique and the elementary aspects of electricity and magnetism, it will supply the real content of a large and important part of the subject.

The first fourth of the book is devoted to the discussion of Maxwell's equations, their general solution in terms of various potentials, and the stress and energy relations in the electromagnetic field. Instead of suddenly pulling the electromagnetic stress tensor out of a concealed hat, the author gives an illuminating outline of the stress and strain relationships in an elastic solid as an introduction. After these preliminary considerations, the second quarter of the book deals with static situations, both electric and magnetic.

The distinctive content is in the last half, where electromagnetic waves are extensively and elegantly treated. Not only simple plane waves, but the important cases of waves guided by conductors of various shapes, waves in cylinders and coaxial lines, standing waves in spheres, and diffraction by spheres are treated thoroughly.

It is of course always possible to point out respects in which some improvement might be made. There is a slight confusion in notation due to departures from some standard symbols. This is certainly difficult to avoid in so extensive a subject. One might also wish for a more extensive and detailed index and more extensive cross references. Furthermore the new m.k.s. system of units is used throughout. This is doubtless an aid to numerical computation, but it tends to obscure the atomic significance of the electric and magnetic properties of material bodies.

These, however, are trivialities. The book will be excellent for a final course in electromagnetic theory and will be of extreme value to all those engaged in the application of the theory, especially in high frequency work.

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California Institute of Technology

Working Stresses

BY JOSEPH MARIN. Pp. 41, Figs. 25, 14×22 cm. Rutgers University Press, New Brunswick, New Jersey, 1940. Price $1.00.

With the more exacting requirements of machine parts design in modern engineering comes the urgent necessity of a better knowledge of limiting stresses and combination of stresses which can be safely used. This little book is an excellent review of our present knowledge of the behavior of engineering materials as regards failure. The subject to which the author himself has added many personal contributions is presented from a practical viewpoint with formulas and diagrams ready to be used in actual design. The formulas apply, of course, mainly to steels and ferrous materials since these are by far the main load-carrying materials in machine design. The case of failure under static combined stresses is first treated, and for ductile materials the two main theories called the shear theory and the distortion energy theory are compared. The case of combined static stresses for brittle materials such as cast iron and concrete is also considered. For fluctuating stresses after a short discussion of the well-known relation for axial stresses and the relation between the average stress and the mean value, the case of combined stresses is taken up for both brittle and ductile materials. For the latter a distortion energy theory is developed and shown to be in good agreement with tests. Great importance is given to the problem of allowable stresses at high temperature, the so-called creep stresses. The following cases are treated: simple tension, pure bending torsion, and combined stresses.

M. A. BIOT
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Introduction to the Kinetic Theory of Gases

BY SIR JAMES JEANS. Pp. 311, Figs. 35, 14×22 cm. The University Press, Cambridge, and Macmillan Company, New York, 1940. Price $3.50.

Many of the admirers of Sir James Jeans' well-known book, *The Dynamical Theory of Gases*, will be surprised to learn that he has written a second book on the same topic. In many respects his first book is considered to be the classical representation of kinetic theory. Still, quite a few students may have pushed it aside, frightened by its heavy mathematical apparatus and by its volume. It would seem that the author himself felt somewhat the same way about it when he decided to rewrite the book—we use his own words—"in a simpler and more physical manner."

This book seems to the reviewer to be superior to any of Sir James Jeans' many pedagogical masterpieces. Undoubtedly the experience which he acquired through writing the first exhaustive textbook has enabled him to represent the essential ideas in the most lucid way in the second. Those who found the first book too heavy will appreciate the new introduction and the expert reader will enjoy its simple clarity and its direct approach.

Many parts of the author's second book are taken word for word from his first book; other parts are shortened and stripped of mathematical details. The topic is restricted to classical theory; radiation and quantum effects are omitted. In order to help the inexperienced reader to find his way through the different modes of approach, the author has added a chapter which gives a preliminary survey of the principal topics treated in the book. This chapter represents a very illuminating orientation on the methods and problems of kinetic theory which certainly will be greatly appreciated. There is but one chapter in which the reader may be disappointed to find only an abbreviated edition of the corresponding parts of the original book—it is the chapter on the general theory of a gas not in a steady state. Here, it seems to the reviewer, the condensation does not help in the understanding, but leaves the reader dissatisfied with underived mathematical expressions and unexplained results.

In all other parts, however, one cannot but admire the ability of the author to explain things with such clarity. One among many examples of Sir James Jeans' unerring ability to find the shortest and most appropriate expression might be quoted here. When explaining the statistical irreversibility by means of the example of heated water, he says: "Speaking loosely it is just as likely that the water will freeze as that it will boil in any specified way. There are, however, so many ways in which the water can boil, all these ways being indistinguishable to us, that we can say that it is practically certain that the water will boil."

VICTOR WEISSKOPF
University of Rochester

M. K. S. Units and Dimensions

BY G. E. M. JAUNCEY AND A. S. LANGSDORF. Pp. 62 +viii, Figs. 5, 14½×22 cm. Macmillan Company, New York, 1940. Price $1.00.

The foreword states that the purposes of this little book are to acquaint electrical engineers and physicists with the meter-kilogram-second system of units, to give reasons for the adoption of the ohm as the fourth basic unit, to describe a proposed m. k. o. s. system, and to discuss the difference between B and H. There has been need for a book to fulfill the first of these purposes. The other purposes are associated with certain misconceptions regarding dimensions. It is unfortunate that these mistakes should again appear in print, and in connection with a new, and we think desirable, system of units.

As an example, we see on page two that "the unit charge of electricity . . . rests upon ideas which cannot be made to fit within a frame of reference built solely on the concepts of mass, length, and time." Is this intended to be a contradiction of the fact that in some systems such as the Gaussian the dimensions of charge are given in terms of length, mass and time only? It would have been sufficient for the authors to show why they favor a form of the equations which is consistent with the use of four fundamental quantities. Their arguments for the use of the ohm as the fourth basic unit are not convincing; but that question has no bearing on the merits of an m. k. s. system.

The question of rationalization is dismissed with no significant arguments, but the authors use the nonrationalized form of equations. The few previously published books which have come to our attention have used the rationalized form. It is very unfortunate to have both forms in use. A little study of this book brings to light some awkward units or names; the "4π weber," the "coulomb/4π," the "m. k. s. oersted," and the "ampere-turn/4π." In the rationalized system it seems a distinct advantage that the corresponding units are weber, coulomb, amp.·turn/m, and amp.·turn.

Except for shortcomings such as those which we have mentioned, this book should be profitable reading for all who need a better acquaintance with m. k. s. units. It is clearly written, not too theoretical, and easily read.

W. H. MICHENER
Carnegie Institute of Technology

Mathematical Theory of Non-Uniform Gases

BY SYDNEY CHAPMAN AND T. G. COWLING. Pp. 404 +xxiii, Figs. 13, 18½×26 cm. University Press, Cambridge, and Macmillan Company, New York, 1939. Price $7.50.

This book may be regarded as a truly important contribution to the literature of physics. For the first time it makes available to all physicists and mathematicians that beautiful structure of logical development based on the original ideas of Maxwell and Boltzmann which we know as the exact theory of transport phenomena in gases. That the theory which is developed in this book has not hitherto played a greater role in the thinking of many physicists has two causes. On the one hand much of the original work has not been readily available. On the other hand excellent treatments based on the concept of the mean free path have been regarded generally as adequate. Such treatments, while lacking in rigor, possess the advantage of achieving clarity of exposition through the use of intuitive concepts. The more rigorous treatment on which this book is based makes sacrifices in this respect, but it leads to results which, in principal at least, may be regarded as accurate.

The aim of the authors is to give a full account of the mathematical theory of viscosity, thermal conduction and diffusion. In one sense this is an ambitious program. Beginning with the fundamental integro-differential equation of Maxwell and Boltzmann one seeks to find explicit expressions for certain mean value quantities as, for example, the components of mass velocity, heat current, and the stress tensor, in terms of the gas parameters and

their spatial derivatives. This end can be reached only through long difficult mathematical arguments. The authors choose to follow the deductive method of Hilbert, Lorentz and Enskog for this purpose rather than the method of Maxwell and Chapman. In carrying out this procedure they have made some simplifications in Enskog's treatment by introducing their notation for three-dimensional Cartesian tensors. The treatment does demand a tensor notation, but there may be some question that the particular notation used achieves the maximum clarity in exposition. A real simplification over the work of Enskog and others lies in the use of Sonine polynomials as the set of functions on the basis of which the necessary series developments are made. This choice of functions has the advantage of simplifying the numerical calculations which must eventually be made, and of putting the results in such a form that the series convergence is readily established.

In another sense the program of this book is not as ambitious as one might like. It is true, as announced by the authors, that the subject is complete in itself. Yet the theory of gases under conditions of non-uniformity is but one aspect of general non-equilibrium theory, and as such belongs to the larger field of statistical mechanics. This is implied by the introduction of a chapter on the H-theorem, and the use of methods analogous to those employed in the proof of this theorem to obtain the zeroth approximation to the solution of the integro-differential equation. But the H-theorem has greater generality than the method of proof which depends upon such limitations on the character of the system as to make possible an explicit expression for dH/dt. It is true that all attempts to generalize the theory of transport to more general systems have been frustrated by insuperable mathematical difficulties as well as unanswered questions regarding the proper method of formulation of the problem. Nevertheless, it seems highly desirable to have the theory of gases, complete in itself though it may be, properly set within the framework of general non-equilibrium theory as we know it.

Throughout the book the arguments and deductions seem to have been made with considerable care and precision. There are, nevertheless, certain statements which raise questions that may be significant. For example, in the chapter on gas mixtures the authors state that the theory will be restricted to binary mixtures since "no essentially different features are introduced when more than two gases are present." The correctness of this statement depends perhaps on one's understanding of the word "essential." There is at least the following difference between binary and more complex mixtures. In the case of the former the fact that the matter currents for the two components are equal and of opposite sign has as its consequence that the force terms for the two components enter into the distribution function with opposite sign. The decomposition of the distribution function into terms depending on forces, the temperature gradient, and the strain tensor then leads to six integral equations in place of the original one. However, for a gas of N components, with $N>2$, the situation is different, and the decomposition leads to $N(N+2)$ integral equations. This circumstance is related to the appearance of the phenomena of induced diffusion for the case of complex mixtures.

Secondly, one might question certain implications which appear in the discussion of the quantum statistics. It is by no means certain that the modifications which are introduced in the collision integral to account for the new statistics are adequate for a description of transport phenomena, except for the case of almost complete undegeneracy. This is true particularly in the Einstein-Bose statistics in which the contributions to transport come quite largely from molecules of low energy.

The authors have succeeded admirably in their attempt "to record the fullest present development of the kinetic theory of gases, based on classical mechanics." All of the mathematically simple molecular models have been considered in the main part of the theoretical development, and in addition a complete chapter is given to the rough spherical model of Pidduck, the one case of a particle possessing internal degrees of freedom for which there is a theory. In addition to the main theoretical development there are chapters on electromagnetic phenomena in ionized gases, the behavior of gases in magnetic fields, and phenomena in strong electric fields. Wherever possible the theoretical results are carefully compared with experimental data. Many will find this tabulation of available data and the collection of formulae derived from the theory of great value.

E. A. UEHLING
University of Washington

Geophysical Prospecting for Oil

BY L. L. NETTLETON. Pp. 444+xi, Figs. 177, 16×23½ cm. McGraw-Hill Book Company, New York, 1940. Price $5.00.

Readers of this journal conversant with developments in geophysics are no doubt aware of the fact that after a period of silence of some ten years, there have been produced, with a simultaneity perplexing to some, three textbooks on geophysical prospecting. Two of these cover the entire field whereas the book under discussion is confined to applications in oil prospecting. All three books have had considerable territory to cover, which accounts for the rather large number of pages in most of them. Having one of these miniature encyclopedias on his conscience, the reviewer is well aware of the infinite amount of labor and patience that go into the preparation of a book of this character and is therefore inclined to view a parallel undertaking with sympathy rather than with prejudice.

Nettleton's book has been carefully prepared. The material is logically arranged, the presentation is clear and coherent, and the text is easy reading. The author has possibly been too modest in stating that the work is intended for the student or the lay reader rather than the specialist, for it may be read with profit by those specializing in one division of geophysics and wishing to familiarize themselves with another. The mathematical discussion can be readily followed. Possibly, an advanced student may consider some of the derivations too expansive. However,

the reviewer has been impressed throughout the book with the author's sincere desire to "put the subject across" in his own words and his own mathematical style. A treatment of this kind is infinitely preferable to one embodying uncritical adaptations of high powered derivations that are neither understood by the author nor the reader—unfortunately, there are some so-called texts in which this procedure is still being followed.

The introduction to the book deals with the accumulation of oil and gives a general review of geophysical methods. This is followed by a section on gravity methods, comprising 7 chapters. Part II, encompassing 5 chapters, covers the magnetic methods whereas Part III, in 6 chapters, gives a discussion of seismic refraction and reflection technique. Part IV, consisting of 3 chapters, is a discussion of electrical prospecting methods, electrical well logging and miscellaneous geophysical methods such as soil and gas analysis, geothermal investigations, radioactivity measurements and well surveying. The book is concluded with a short chapter on the interpretation of geophysical results. In each section, the treatment is uniform, beginning with an explanation of fundamental principles, followed by a discussion of the relationship between the method under discussion and the corresponding method in geophysical science. Then comes a description of instruments and procedures and of reduction methods, the section being concluded with a discussion of calculation and interpretation methods. The author has made a serious effort everywhere to present complex matter in as simple language as possible. Analogies are well chosen, and the text as a whole reflects the author's experience in teaching the subject.

Printing is clear, illustrations are good and the lettering is legible. The stock is heavy enough to assure good reproduction of halftones. The index comprises 16 pages. References are given in footnotes by author's name and year and refer in turn to bibliographies at the end of each section. This entails some duplication and it would appear preferable to refer to the bibliography by number or quote the entire reference in the footnote.

There is one suggestion for improvement the reviewer would like to make. At present, the book contains no illustrations whatever of actual geophysical surveys. Field results on established geologic conditions are the best demonstration of geophysical principles, just as experiments in the physical laboratory furnish "the proof of the pudding" for the deductions of the theoretical physicist. There is no doubt that the student and the professional geologist would grasp the meaning of geophysical data much better if they were presented together with the corresponding actual geologic conditions. An inspection of actual field data would enable the reader to judge for himself to what extent theoretical relationships are applicable and which geologic factors modify or limit the ideal response to subsurface conditions.

The reviewer has enjoyed reading this book with its conservative and lucid style and does not hesitate to recommend it to all students of geophysical oil exploration.

C. A. HEILAND
Colorado School of Mines

Statistical Mechanics

BY JOSEPH EDWARD MAYER AND MARIA GOEPPERT MAYER. Pp. 495+xi, Figs. 30, 15×23½ cm. John Wiley and Sons, Inc., New York, 1940. Price $5.50.

This book fills an important gap in the recent literature on statistical mechanics. It is written for readers who are interested in the understanding of the applications of statistical mechanics and who wish to be introduced into the fundamental laws as directly and as simply as possible, without much concern as to the many subtle and far-reaching problems connected with the principles of statistical mechanics. It is therefore entirely distinct from other recent books on the same subject as, for example, the excellent books by Tolman and by Landau, since it avoids as much as possible the use of abstract theoretical methods. Quantum theory is introduced right from the start and it is interesting to note that the use of quantum language considerably simplifies many fundamental considerations.

The book contains introductory chapters on kinetic gas theory and on mechanical and quantum theoretical preliminaries and proceeds then to the definition of the fundamental statistical concepts and to the derivation of the thermodynamic laws. The following chapters are devoted to mono- and polyatomic perfect gases and to chemical equilibria in gas mixtures. The problems involving perfect gases are treated by means of the Boltzmann method which considers the energy and not the temperature of the gas as exactly determined. In order to treat systems composed of dependent particles the Gibbs method of canonic ensembles is introduced and it is shown that the same results are obtained if it is applied to perfect gases. The crystalline solid, the imperfect gases, and conduction phenomena are then treated in great detail with special emphasis on the well-known work of the authors on condensation. Two chapters on dielectric and diamagnetic phenomena and on degenerate gases conclude the book, the latter containing as examples a treatment of the black-body radiation and of the electron gas in metals.

The promise given in the preface: ". . . to present this subject in a simple manner to make it easily available to scientists whose familiarity with theoretical physics is limited," is well kept throughout the volume and it is certain that this book will be widely used and appreciated by chemists and physicists.

VICTOR WEISSKOPF
University of Rochester

German-English Science Dictionary

LOUIS DE VRIES. Pp. 473, 13×18½ cm. McGraw-Hill Book Company, Inc., New York, 1939. Price $3.00.

This is a convenient, well-printed and well-bound German-English dictionary, arranged particularly for students in the agricultural, biological and physical sciences. It appears to contain most of the technical words and compound words which a physicist is likely to meet in the reading of German texts and periodicals.

Integration of Ordinary Differential Equations

By E. L. Ince. Pp. 148+viii, 12½×19 cm. Oliver and Boyd, Edinburgh, 1939. (Interscience Publishers, New York.) Price $1.50.

This is a textbook suitable for use in the usual elementary courses in differential equations. The first five chapters deal with the methods for solving equations of various standard types in finite form. Chapter III contains an especially good geometrical discussion of equations of the first order and of higher degree than the first. Chapter VI is devoted to the solution of differential equations by means of infinite series. Frobenius' method for obtaining solutions of linear equations in the neighborhoods of regular singularities is described, and is applied to the hypergeometric equation and the equations of Legendre and Bessel. 300 exercises are given.

The book contains a large amount of information in a small space, and is to be warmly recommended. The reviewer would have preferred to see more extensive treatments of the method of variation of constants and of systems of linear equations, perhaps at the expense of some of the "operator theory" in Chapter V.

L. A. MacColl
Bell Telephone Laboratories, Inc.

Determinants and Matrices

By A. C. Aitken. Pp. 135+vii, 12½×19 cm. Oliver and Boyd, Edinburgh, 1939. (Interscience Publishers, New York.) Price $1.50.

In this book the fundamental rules of matrix algebra and the properties of determinants are developed from the beginning. Although the treatment is rigorous, it may be readily understood by a reader acquainted with engineering mathematics.

The simpler operations of matrix algebra are explained in the first chapter. Chapter two defines determinants and their simpler properties are derived. Chapter three introduces reciprocal matrices and the solution of simultaneous linear equations is thoroughly treated. Various expansions of determinants are given in chapter four. The remaining two chapters discuss special types of matrices and determinants. Several related topics including various identities connecting the minors of a determinant, symmetric functions, and dialytic elimination are also discussed. Many illustrative problems are given in the text.

S. O. Rice
Bell Telephone Laboratories, Inc.

Vector Methods

By D. E. Rutherford. Pp. 127+viii, Figs. 16, 12½×19 cm. Oliver and Boyd, Edinburgh, 1939. (Interscience Publishers, New York.) Price $1.50.

Although the author has intended this book for the use of undergraduate students, it will be welcomed by those already engaged in scientific and engineering work. In some fields of applied science and engineering, understanding of vector concepts is indispensable and moderate knowledge of vector algebra is helpful. This book contains the most essential information.

Fourteen pages are devoted to vector algebra and seventeen to the gradient, the divergence and the curl; the methods are then illustrated by applications to differential geometry, mechanics, potential theory and hydrodynamics in a series of chapters from ten to twenty pages long. The author has even found room for nine pages of four-dimensional vector analysis.

S. A. Schelkunoff
Bell Telephone Laboratories, Inc.

Statistical Mathematics

By A. C. Aitken. Pp. 153+vii, Figs. 17, 12½×19 cm. Oliver and Boyd, Edinburgh, 1939. (Interscience Publishers, New York.) Price $1.50.

This clear, concise survey of the mathematical basis of statistics presumes a knowledge of algebra up to the binomial theorem and the simpler infinite series, and of elementary calculus. It treats, with a marvel of compression and from a modern viewpoint, the concept of probability, the most common probability distributions, the elements of correlation, partial correlation, and regression, the sampling distributions of the simpler statistics, and comments on the problem of estimation. Elegance and brevity are attained by the introduction of the generating function in some of its most important forms. The book should be of great value to the physicist, chemist, or engineer interested in attaining with minimum effort a sound introduction to mathematical statistics.

Walter A. Shewhart
Bell Telephone Laboratories, Inc.

Integration

By R. P. Gillespie. Pp. 126+viii, Figs. 10, 12½×19 cm. Oliver and Boyd, Edinburgh, 1939. (Interscience Publishers, New York.) Price $1.50.

This little volume is a textbook of a novel kind. The first four chapters give an exposition of integration which is similar in character and scope to those found in the usual elementary calculus texts. The last three chapters give a concise introduction to the Riemann theory of integration. In these chapters various fundamental theorems of analysis, such as the theorem that a function which is continuous in a closed interval is uniformly continuous in the interval, are stated and used without proof. Also, attention is confined to comparatively well-behaved functions. The book contains numerous good exercises.

The exposition is clear and pleasing; and the rigor in the latter part is satisfactory on the whole, although a few lapses were noticed. The book should be useful to students of physics and engineering who wish to deepen their knowledge of integration without reading one of the more exhaustive treatises.

L. A. MacColl
Bell Telephone Laboratories, Inc.

Theory of Equations

By H. W. Turnbull, F.R.S. Pp. 152+xii, Figs. 24, 12½×19 cm. Oliver and Boyd, Edinburgh, 1939. (Interscience Publishers, New York.) Price $1.50.

This concise little book covers essential topics of college algebra and presents them in an interesting, competent, and straightforward manner. It will prove useful to a variety of readers, those concerned in applications of mathematics to science and engineering as well as to students of mathematics.

Complex numbers, evaluation of polynomials, partial fractions, the fundamental theorem of algebra, symmetric functions, numerical solution of equations, location of the roots, cubic and quartic equations are taken up in various chapters.

S. A. Schelkunoff
Bell Telephone Laboratories, Inc.

Television Receiving Equipment

By W. T. Cocking. Pp. 298+viii, Figs. 174, 12×18½ cm. Nordeman Publishing Company, New York. (Published by The Wireless World, England), 1940. Price $2.25 per volume.

This book is written primarily from the viewpoint of the advanced experimenter who is interested in the design of television receivers principally from the practical side, but who would also like to know the theory of operation of the various circuits. No time is spent in reviewing the history of television development, and only the requirements of cathode-ray tube receivers are considered.

After a brief discussion of the general principles of television the author immediately takes up the requirements of the special circuits used in television receivers. It is assumed that the reader is familiar with the circuits and operation of sound receivers and, based on this, the practical differences between sound receivers and television receivers are brought out. New circuits required for television, such as deflecting circuits, synchronizing separation and video frequency amplifiers are discussed in particular detail.

It is unfortunate, from the American point of view, that the book is so solidly based on the English television system and on the standards used in the Alexandria Palace transmissions. All of the numerical examples given are based on these standards which are, in many respects, considerably different from those used in this country.

The general functions which the television receiver must perform are, however, the same for either American or British standards, and if the specific differences are kept in mind the book will be found to be quite useful. It is especially to be recommended for the completeness with which it covers the field. In each case several methods of accomplishing specific functions are discussed, and the advantages and disadvantages of each are brought out. There are frequent references in footnotes, mostly to articles in *The Wireless World*.

R. S. Holmes
RCA Manufacturing Company, Inc.

Here and There

Technologists Needed

The United States Civil Service Commission announces open competitive examinations (unassembled) for the following positions in such specialized branches as explosives, fuels, plastics, rubber, minerals, textiles, or any other well-defined specialized branch: Principal Technologist, Senior Technologist, Technologist, Associate Technologist, and Assistant Technologist. Applications will be rated as received at the United States Civil Service Commission, Washington, D. C., until December 31, 1941, and certification made as the needs of the service require, except that, if sufficient eligibles are obtained, the receipt of applications may be closed, in which case due notice will be given. The Commission, according to its announcement, is at present experiencing difficulty in filling technologist positions in specialized branches, and applicants possessing qualifications in these branches are urged to file their applications.

★

New Laboratory Plant

Constructed in the modern daylight type of architecture with ample skylight and window areas, the new building of the G-M Laboratories, Inc., located at 4314-26 North Knox Avenue, Chicago, has been recently completed and is shown in the accompanying photograph. This new plant

is planned to serve the needs of production of precision instruments, such as G-M's latest photoelectric product, the new G-M Standard Exposure Meter. Fifteen years ago Dr. Lee DeForest, who was then pioneering in his work on "sound-on-film" for movie projectors, delegated G-M Laboratories, Inc., to create a photoelectric cell for this specific purpose. From this beginning G-M Laboratories have become one of the foremost concerns in America manufacturing photoelectric cells on a commercial scale.

★

Professor W. L. Bragg, F. R. S., Cavendish Professor of Experimental Physics in the University of Cambridge, England, is listed among the names of scientific men and others associated with scientific work appearing in the New Year Honours List of England, printed recently in *Nature*.

Order of Lenin Award

For his outstanding work in physics, Professor A. F. Joffe has been awarded the Order of Lenin, the highest honor in the Soviet Union, *Nature* reports. Presented on the occasion of Professor Joffe's sixtieth birthday, this award recognizes his work on mechanical and electrical properties of crystals, on the photoelectric effect and the magnetic field of projectiles, and on semi-conductors. Under the guidance of Professor Joffe, experiments have been carried out which resulted in the increase of frost-resistance of Soviet-grown caoutchouc and in a new method for the manufacture of plastic synthetic rubber. He was responsible for the establishment of the Physico-Technical Institute in Leningrad in 1918, the first of a system of physico-technical and physico-chemical institutes in the Soviet Union, the announcement in *Nature* states.

★

Moscow Plans 50-Million Volt Cyclotron

The construction of a very powerful cyclotron, capable of producing 50-million electron volt deuterons, will be commenced in Moscow early in 1941, according to a decision of the Academy of Sciences of the U.S.S.R., based on a report submitted by the Physical Institute of the Academy. A magnet, the core of which weighs about 1,000 tons and solenoid of 18 tons, is to be installed. A special building to house the cyclotron will be erected in the grounds of the new home of the Physical Institute of the Academy being built on the Bolshaya Kaluzhskaya Ulitsa in Moscow. The old apparatus in the Soviet Union, which is in the Radium Institute of Leningrad, is capable of giving an energy of 4-million electron volts to particles; another, nearing completion at the Physico-Technical Institute, also in Leningrad, will be capable of imparting an energy of 10–12-million electron volts.

Nature

★

George de Hevesy, of the Institute of Theoretical Physics of the University of Copenhagen, has been appointed Durham lecturer at the Harvard Medical School for the present academic year. He will deliver a series of lectures open to the public, beginning on April 28, on the "Application of Radioactive Isotopes to Biological Problems."

Science

★

Dr. S. A. Goudsmit, Professor of Physics at the University of Michigan, has been granted a leave of absence for the second semester, according to a note in *Science*. Dr. Goudsmit is conducting graduate courses at Harvard University.

★

Professor Ernest Franklin Barker, of the University of Michigan, has been appointed Chairman of the Department of Physics, a recent issue of *Science* states. He assumed his duties as Chairman on February 17, taking the place of Professor Harrison M. Randall, who has retired from active service.

Necrology

Professor Dayton C. Miller, who last year completed 50 years of service to Case School of Applied Science, died on February 22, 1941, at the age of 74 years. Dr. Miller was Secretary of the American Physical Society from 1918 to 1922 and President of the Society in 1925 and 1926. He held the secretaryship of Sigma Xi from 1912 to 1914 and served on the Council of Sigma Xi in 1935. Distinguishing himself in the fields both of acoustics and optics, Dr. Miller's contributions to science included research in the following subjects: the velocity of light in a magnetic field, expansion of gases, Roentgen rays, relative motion of the earth and ether, efficiency of incandescent gas light, interferometer applications, photographic registration of sound waves, and quality of musical sounds.

★

Physics Staff Enlarged

Recent additions to the physics staff of the Armour Research Foundation are Dr. C. N. Challacombe, formerly of the Physics Department of Baker University in Baldwin, Kansas; and Dr. E. W. Landen, previously with the Physics Department of William Jewell College and the University of Missouri. Dr. Challacombe and Dr. Landen will be associated with Dr. George Ziegler, Director of the Light Division of the Armour Research Foundation, in the investigation of industrial problems related to light and optics.

Instrument Booklets

Wave - length - density and wave - length - transmission curves for twenty-seven types of Bausch and Lomb colored glass filters constitute a large section of the 62-page descriptive booklet on "Colored Glass Filters" issued by the Bausch and Lomb Optical Company, Rochester, New York. In the section preceding the graphs, properties of filters are discussed.

Applications for Cenco Industrial Fellowships are invited through an announcement in the January, 1941, issue of *Cenco News Chats*, publication of the Central Scientific Company, 1700 Irving Park Road, Chicago, Illinois. Appointment of two or possibly three Cenco Industrial Fellows will be made in April. Applicants should be candidates for the Bachelor's degree in June, 1941, with a physics major and with chemistry and mathematics as minors, or a chemistry major with physics and mathematics as minors.

The catalog, "College Texts and Reference Books in Science, 1941–1942," distributed by Longmans, Green and Company, 55 Fifth Avenue, New York, lists physics books in the following fields: general physics; mechanics; electricity and magnetism; heat and thermodynamics; optics, light and color; photography; spectroscopy; sound; advanced physics; and several miscellaneous fields.

Contributors to This Issue

G. Failla

G. Failla was graduated from Columbia University with the degree of E.E. in 1915 and M.A. in 1917. He received the D.Sc. degree from the University of Paris in 1923. Dr. Failla has been in charge of the Physics Department at Memorial Hospital, New York City, for many years.

Robley D. Evans, after receiving the Ph.D. degree from the California Institute of Technology in 1932, spent the next two years as National Research Fellow at Berkeley. In 1937 he received the Theobald Smith Award in the Medical Sciences, which is administered by the American Association for the Advancement of Science, for physical techniques and measurements on radium poisoning. Dr. Evans is now Associate Professor of Physics at the Massachusetts Institute of Technology.

Harold C. Urey, the discoverer of heavy hydrogen, is Nobel Laureate in Chemistry for 1934. After receiving his Ph.D. degree from the University of California in 1923, he was an American Scandinavian Foundation Fellow in Denmark, studying in the institute of Professor Bohr. From 1924–29 he was Associate in Chemistry at Johns Hopkins University, and since then he has been Associate Professor, Professor and Executive Officer of the Department of Chemistry at Columbia University.

H. C. Urey

R. D. Evans

Calendar of Meetings

April

4– 5 Southeastern Section, American Physical Society, Nashville, Tennessee
5 New York State Section, American Physical Society, Oneonta, New York
7–11 American Chemical Society, St. Louis, Missouri
16–19 Electrochemical Society, Inc., Cleveland, Ohio
23–25 American Society of Civil Engineers, Baltimore, Maryland
23–25 American Mining and Metallurgical Engineers, Chicago, Illinois
28–30 National Academy of Sciences, Washington, D. C.
30–May 3 American Geophysical Union, Washington, D. C.

May

1– 3 American Physical Society, Washington, D. C.
5– 7 Acoustical Society of America, Rochester, New York
5– 7 Society of Motion Picture Engineers, Rochester, New York
12–15 American Foundrymen's Association, New York, New York
12–21 American Institute of Chemical Engineers, Chicago, Illinois
19–23 American Society for Metals, Los Angeles, California
27–29 American Society for Refrigerating Engineers, Cincinnati, Ohio

June

1– 6 Society of Automotive Engineers, White Sulphur Springs, West Virginia
2– 6 American Medical Association, Cleveland, Ohio
12–20 American Society of Mechanical Engineers—Semi-Annual, Kansas City, Missouri
16–19 American Society of Heating and Ventilating Engineers, San Francisco, California
16–20 American Institute of Electrical Engineers (Summer Convention), Toronto, Ontario
18–20 American Physical Society, Pacific Coast Meeting, Pasadena, California
19–21 National Colloid Symposium, Cornell University, Ithaca, New York
20–21 American Physical Society, Providence, Rhode Island
23–27 American Association for the Advancement of Science, Durham, New Hampshire
23–27 American Society for Testing Materials—Annual Meeting and Exhibit of Testing Apparatus and Related Equipment, Chicago, Illinois

"WRATTEN LIGHT FILTERS"

A Book of Data on Wratten Filters

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The 88-page Sixteenth Edition of this publication gives transmission curves and tables for all filters, as well as notes on the use of filters for special purposes. It is available at dealers in photographic supplies—the price is 50 cents.

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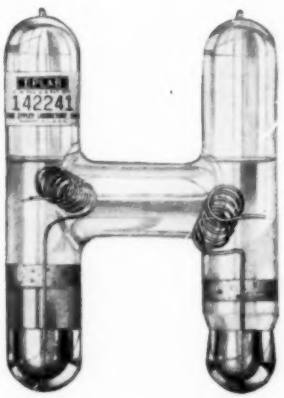

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SCIENTIFIC INSTRUMENTS

NEWPORT, R.I.

U.S.A.

Innovations in Instruments

Four-Range Rheostat

Two closely bifilar wound windings, constructed so that each turn of one winding runs between two turns of the other winding, are incorporated in the Rex four-range rheostats, one model of which is shown in the accompanying figure. This unit takes the place of four individual rheostats. Both windings, operated by one slider with lubricated contacts, consist of two wires of identical diameter

made of materials having different specific ohmic resistances, such as nickel-copper and nickel-chrome alloy. The resistance materials are insulated with Fiberglas, a material retaining satisfactory dielectric strength at the temperature reached when the rheostat is fully loaded. This instrument is marketed by the Rex Rheostat Company, 37 West 20th Street, New York, New York.

Tests Rubbing Abrasion Resistance

Useful as a testing machine for evaluating resistance to rubbing abrasion of surface finished such as paints, lacquers, electroplated and plastic surfaces and textile fabrics of all kinds, the Research Model Taber Abraser has been recently marketed by The Taber Instrument Company, North Tonawanda, New York. The primary elements of the abraser are the motor-driven turntable on which the specimen is mounted, a counter to indicate the number of abrasion cycles, and two abrading wheels that alternately rub back and forth, and at the same time, criss-cross in their rolling path. These wheels are made in five types of closely controlled resilient material charged with special grades of fine abrasive grain. The pivoted arms without auxiliary weights apply a pressure against the specimen of 500 grams per wheel which is recommended for general use on textile fabrics. The addition of the auxiliary weights increases the pressures to 1000 grams, the standard for longer wearing materials.

Aeropressure Microphone

A new aeropressure microphone whose directional characteristics may be changed at will by the use of a new "paracoustic" reflector baffle attachment, has been announced by George Ewald, Manager of the Commercial Sound Division of the RCA Manufacturing Company. The microphone is suited for all types of public address applications, as well as for amateur radio-telephone transmitters. The microphone is designed primarily to withstand the wind and weather conditions found in outdoor applications, though it is equally well suited for indoor use, especially under conditions demanding low cost and ability to withstand rough usage. Available in both low impedance (250 ohms) and high impedance (40,000 ohms) models, it employs a new type of plastic diaphragm for maximum ruggedness, and is equipped with a 30-foot cable.

New Tubes

The following new tubes have been made available recently by the RCA Manufacturing Company, Inc., according to an announcement originating in the RCA Radiotron Division, Harrison, New Jersey:

RCA-1629, a high vacuum, heater-cathode type of tube designed to indicate visually, by means of a fluorescent target, the effects of a change in the controlling voltage. The tube, therefore, is essentially a voltage indicator and as such is particularly useful as a convenient and non-mechanical means of indicating accurate adjustment of a circuit to the desired conditions. Because of its 12.6-volt heater and its 7-pin base, the 1629 is particularly suitable for service in aircraft radio equipment.

RCA-8000, a transmitting triode having a maximum plate dissipation of 150 watts under ICAS conditions. In self-rectifying oscillator circuits, such as are often used in therapeutic applications, two 8000's are capable of delivering a useful power output (at 85 percent circuit efficiency) of 550 watts. The 8000 is rated for operation with full input at frequencies up to 30 megacycles, but it may be used with reduced plate voltage and input at higher frequencies up to 100 megacycles.

Sealing Technique Patented

Kovar, a mixture of iron, nickel, cobalt and manganese, having the same thermal expansion as glass, is now being used in a new way to seal parts of vacuum tubes used in the radio and electric power industries, according to an announcement of the Westinghouse Electric and Manufacturing Company, East Pittsburgh, Pennsylvania. This new sealing technique, patented by Howard Scott, research engineer of Westinghouse, is used in conjunction with hard, low expanding types of glass. It is well suited to the work of joining metal and glass parts of x-ray tubes and ignitrons, efficient devices for changing large amounts of alternating current to direct current for industrial purposes. One company is using Kovar to seal the glass windows into gas meters. A type of thermometer now used widely in aircraft engines has a fine Kovar wire entirely imbedded in glass.

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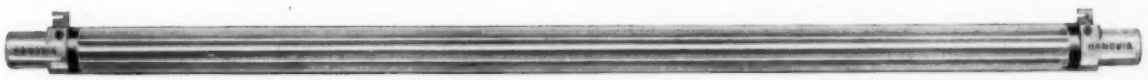

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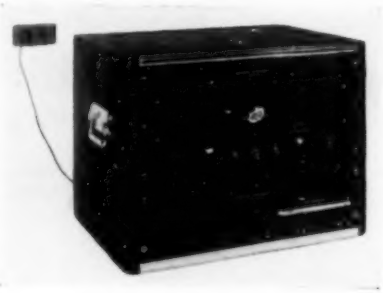
INNOVATIONS IN INSTRUMENTS (CONTINUED)

Tuning Fork Controlled Time Standard

An Aminco Time Standard, consisting essentially of an electronically driven 500-cycle tuning fork and an electrically isolated pick-up and power amplifier as the source of the output power, has been announced recently by the American Instrument Company, 8010–8020 Georgia Avenue, Silver Spring, Maryland. This instrument is shown in the accompanying photograph. The frequency of the tuning fork in the model marketed is 500 cycles per second ±0.2 percent at 25°C. A thermometer on the front panel



of the instrument indicates the temperature of the air in the fork compartment through the range of 10°C to 50°C and can be read to 0.1°C. The temperature coefficient of frequency of the fork is −0.012 percent per °C. The output is in the form of undistorted sine-wave power, continuously variable from 0 to 2½ watts. The push-pull amplifiers are rated at 10 watts maximum output, and the final output transformer has a power rating of 20 watts. Output impedances of 4, 8, 15, and 500 ohms are available.

New Three-Lite Photo-Enlarger Lamp

Rated at 50–100–150 watts, a new "three-lite" photo-enlarger lamp, about the size of a conventional 50-watt bulb, has just been announced by the Westinghouse Lamp Division, Bloomfield, New Jersey. This new lamp, illustrated here, contains two filaments; various settings of the switch turn on either or both filaments. Average life of each filament is 100 hours. The lamp has a three-contact medium screw base which requires a special socket. Since external size of the socket is the same, however, it may replace the conventional type of socket. The three-lite photo-enlarger lamp accommodates the increasing variety of printing papers and negative sizes with which photographers work.

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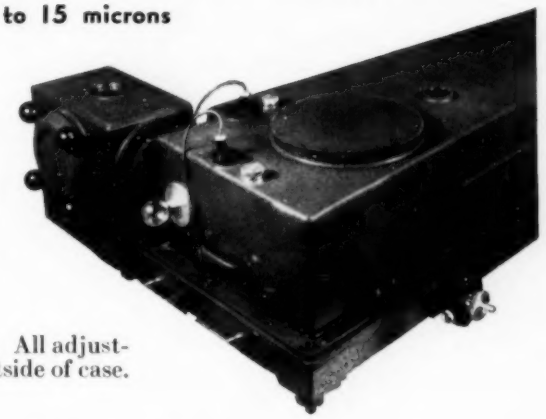

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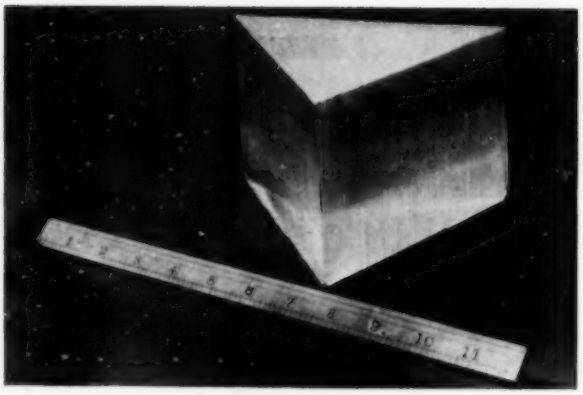

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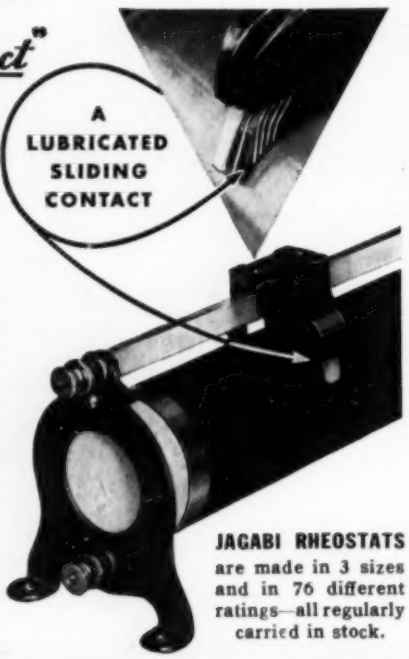

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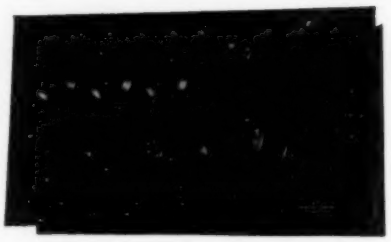

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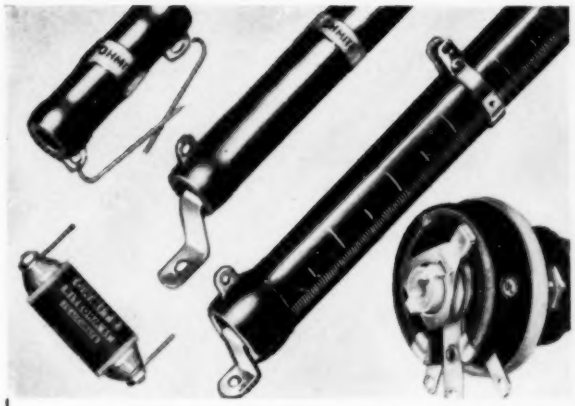

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